A PROSPECTIVE EVALUATION OF THE IMPLANTABLE CARDIOVERTER DEFIBRILLATOR: FACTORS AFFECTING IMPLANT SUCCESS, OUTCOME, THERAPY DELIVERY, SOCIAL ADJUSTMENT AND COST EFFICACY.

MARK ANDERSON

Department of Cardiological Sciences

St. George's Hospital Medical School

University of London

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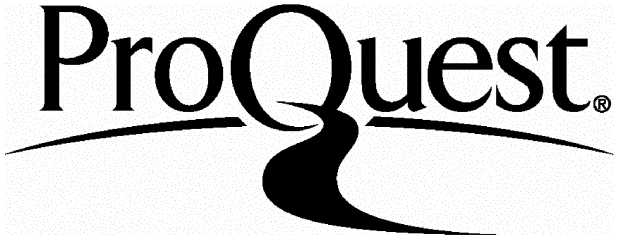

ABSTRACT:

The Implantable Cardioverter Defibrillator (ICD) offers an alternative to drug therapy, surgery or catheter ablation for the treatment of patients with life threatening ventricular tachyarrhythmias. This thesis reviews the development and current status of this therapy with reference to the first 48 patients to receive an ICD at St. George's Hospital. Data from these patients has been used to analyse the factors affecting success or failure of ICD implantation using a transvenous lead system, the patterns of ICD therapy delivery, long-term device performance and occurrence of complications. Using novel techniques for assessment of psychomotor performance and cerebral blood flow the impact of continuing transient episodes of arrhythmia on motor performance was studied. Risk analysis techniques have been applied to examine whether ICD recipients should be allowed to drive a motor vehicle and a flexible model has been developed by the author to enable the assessment of the cost-efficacy of ICD use in its present and potential future applications.

The study concludes that smaller heart size on the chest radiograph is the best predictor of successful ICD implantation using a transvenous lead system and that low left ventricular ejection fraction is the best predictor of appropriate ICD therapy delivery. The psychomotor studies show that even transient hypotensive symptoms during an arrhythmia are associated with marked impairment of psychomotor performance. Risk analysis shows that ICD patients who have not received a therapy within the two years after ICD implant might safely be allowed to drive a private motor vehicle.

Modelling techniques show that the current use of the ICD in high-risk cardiac arrest survivors is comparable in cost-efficacy to other invasive medical therapies. Relative reductions in equipment cost, increasing ICD life and reduced implant mortality could result in a fourfold improvement in cost-efficacy over the next decade. Prophylactic use of the ICD may prove cost-effective in the light of these changes but has major implications for health care expenditure because of the large numbers of ICD implants required.

TABLE OF CONTENTS:

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CHAPTER 1:

INTRODUCTION

PART I: SUDDEN CARDIAC DEATH, DEFIBRILLATION AND THE IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

Epidemiology and mechanism of sudden death:

The recognition that cardiac arrhythmias could cause sudden death is not new. As long ago as 1889 John McWilliam, whilst reviewing the subject of sudden death wrote that ".... it is very probable that in many of these cases the fatal issue is determined or ensured by the occurrence of fibrillar contraction in the ventricles."

Sudden death is now recognised as a common mode of death in the Western world with approximately 400,000 such deaths per annum in the United States (Gordon & Kannel 1971, National Center for Health Statistics 1981). It is the commonest mode of death in men aged between 20 and 60 years. The majority of such sudden deaths appear to be due to cardiac disease and particularly coronary artery disease. Evidence from community studies such as the Wandsworth study (Thomas *et al.* 1988) suggest that ischaemic heart disease is responsible for 65% of sudden deaths in men and 41% in women. Nonischaemic cardiac disease was responsible for 5.9% of deaths in men and 11.9% in women.

In the United Kingdom there is no definitive figure for sudden cardiac death but about 30,000 ischaemic heart disease deaths occur outside the home or hospital each year (Silman AJ 1981). It is likely that the majority of these are sudden and of course some deaths occurring at home will also be sudden. Extrapolation from the per capita figure for the United States would suggest around 60,000 sudden deaths in the United Kingdom per

annum. What is not clear from such figures is the proportion of these sudden deaths which are directly due to a cardiac arrhythmia, at least in part due to the lack of a universally accepted precise definition of sudden cardiac death (Goldstein S 1982). The most widely used definition is that of unexpected death occurring within one hour of symptoms but other studies have used periods of two (Helmers *et al.* 1976) or 24 hours (Schroeder *et al.* 1980). Such temporal definitions of sudden death overlook the underlying mechanism of death. Hinkle and Thaler (1982) published a classic study of the mechanism of sudden death compared with temporal criteria of classification in 142 deaths amongst a population of 743 men. Fifty-eight of the deaths (40.1%) occurred within one hour of the onset of symptoms and 91.3% of these were classified as arrhythmic. The Cardiac Arrhythmia Pilot Study (Greene *et al.* 1989) also addressed this issue. In this study 3 (13%) of 23 arrhythmic deaths occurred >1 hour after the onset of symptoms and 9 (41%) of 22 nonarrhythmic deaths occurred <1 hour after onset of symptoms. These figures would suggest that the number of arrhythmic deaths is approximately 80-90% of the total for sudden death. Absolute confirmation that sudden death is arrhythmic in origin can only be obtained from fortuitous Holter recordings during which unexpected sudden death has occurred (Pratt *et al.* 1983, Milner *et al.* 1985, Wang *et al.* 1986, Leclerq *et al.* 1988, Bayés de Luna *et al.* 1989, Olshausen *et al.* 1991). Although the final cardiac rhythm in patients dying in hospital of noncardiac causes is predominantly bradyarrhythmic (Wang *et al.* 1986) around 85% of ambulatory sudden deaths occurring during Holter recording are due to ventricular tachyarrhythmias (Bayés de Luna *et al.* 1989).

The underlying mechanism which precipitates the terminal arrhythmia is of some importance because it determines the preventive strategies which may be applied. If all sudden cardiac deaths are due to arrhythmias occurring in the acute phase of a myocardial infarction therapies directed primarily at prevention or treatment of the arrhythmias may have less impact on overall mortality than if the arrhythmias occur on a background of stable

chronic coronary artery disease. Several early studies (Friedman *et al.* 1973, Baum *et al.* 1974, Liberthson *et al.* 1974) suggested that acute myocardial infarction was responsible for 50-60% of episodes and although the remaining patients showed no evidence of acute infarction 90% had evidence of coronary artery disease (Friedman *et al.* 1983) and half of these had evidence of old infarction. Myerburg *et al.* (1980) found evidence of acute infarction by electrocardiographic or enzymatic criteria in 36% of resuscitated cardiac arrest survivors. In a recent meticulous study of 168 cases of sudden cardiac death (defined as death within six hours of the onset of symptoms) evidence of occlusive thrombus or significant mural thrombus was found in 73.3% of cases (Davies MJ 1992). Intramural thrombus associated with plaque fissuring was found in a further 20% of patients but this was also found in 9% of patients whose cause of death was clearly noncardiac.

Thus although acute coronary thrombosis causing myocardial infarction is an important mechanism of sudden cardiac death it accounts for only a proportion of sudden deaths, even in patients with coronary artery disease. Other factors which may be involved in the genesis of arrhythmias in these patients include ischaemia, autonomic nervous system activity and an abnormal substrate due to old infarction. Reversible myocardial ischaemia and especially silent ischaemia may have an important role to play in triggering arrhythmias but this has been hard to prove. The increased incidence of sudden cardiac death during vigorous exercise, especially in patients with coronary artery disease is well known (Siscovick *et al.* 1984). In a small percentage of cardiac arrest survivors with normal coronary arteries arrhythmias may be directly due to silent ischaemia precipitated by coronary artery spasm (Myerburg *et al.* 1992). However silent ischaemia more commonly occurs in patients with underlying coronary disease. Although coronary artery bypass grafting reduces the recurrence rate of cardiac arrest (Every *et al.* 1992) the evidence that it does so by reducing the ischaemic burden is poor. In particular there is no evidence that coronary revascularisation reduces the severity of exercise induced arrhythmias (Mathes P 1987). Whether reversible

ischaemia has a significant role to play in the genesis of sudden cardiac death or whether it is purely a bystander phenomenon remains unclear.

Interest in the role of the autonomic nervous system in determining outcome dates back to 1978 when Wolf *et al.* showed that heart rate variability was reduced in patients with a higher in-hospital mortality after myocardial infarction. More recently the risk of arrhythmic events and sudden cardiac death in post-infarction patients has been found to be higher in patients with reduced heart rate variability (Kleiger *et al.* 1987) and depressed baroreflex sensitivity (La Rovere *et al.* 1988, Farrell *et al.* 1992). Localized myocardial autonomic denervation follows myocardial infarction in dogs and man and is likely to be important in spontaneous arrhythmias and the proarrhythmic effect of some drugs (Stanton *et al.* 1989, 1991). Adrenergic activity is known to be important in triggering of ventricular extrasystoles (Coumel P 1989) and the observation that ß-blockers reduce mortality and also sudden death following myocardial infarction (May GS 1983) further suggests an important role for the autonomic nervous system in the genesis of post-infarction arrhythmias.

Evidence for the role of an abnormal substrate due to old myocardial infarction comes from studies of the signal-averaged ECG. The occurrence of low amplitude signals late in the QRS complex appears to indicate the presence of fractionation and slow conduction within the ventricle and has been shown to be associated with an increased incidence of ventricular arrhythmias (Simson MB 1981, Cripps *et al.* 1988) and sudden death (Gomes *et al.* 1987).

Apart from coronary artery disease a number of other conditions are associated with a relatively high incidence of sudden cardiac death. Hypertrophic cardiomyopathy is associated with a 2-4% annual sudden death rate and in the presence of ventricular tachycardia on Holter monitoring this annual incidence of sudden death may rise to 9% (McKenna *et al.* 1981). Sarcoidosis may be associated with ventricular arrhythmias and sudden arrhythmic death (Winters *et al.* 1991). Patients with the long QT syndrome who present with syncope have a three-year risk of sudden cardiac death of 26% in the absence of therapy with ß-

blocking agents (Schwartz & Locati 1985). The role of conditions such as sudden unexplained nocturnal death (SUND, *lai tai*) and idiopathic ventricular fibrillation remains the subject of debate (Viskin & Belhassen 1990, Nimmannit *et al.* 1991, Almendral *et al.* 1992).

Whilst it is clear that the majority of sudden cardiac deaths occur in patients with coronary artery disease, either due to a new ischaemic event or to the interaction of impaired autonomic nervous system activity with an abnormal substrate, a number of other conditions may be identified which are associated with a high incidence of sudden cardiac death, although their contribution to the total population burden of sudden death is small.

There are thus two approaches which may be adopted in our attempts to reduce premature mortality from sudden cardiac death. The primary, preventive approach is to attempt to reduce the incidence of coronary artery disease by manipulation of risk factors. The secondary approach is to prevent sudden death occurring in those patients who are already at risk either by prevention of the arrhythmias which cause sudden cardiac death or by prompt intervention when they occur.

The History of Defibrillation:

Nearly fifty years have passed since the first well documented report of successful human defibrillation (Beck *et al.* 1947). Closed-chest defibrillation was first reported by Kouwenhoven *et al.*(1954) and clinically applied and refined by Zoll *et al.*(1956, 1960) and Lown *et al.*(1962). Initially defibrillators used a pulse of alternating current at mains voltage but this was replaced by the use of a capacitor discharge.

These developments made defibrillation of patients in hospital a practical therapy. However, the majority of sudden deaths occur outside hospital and it was a logical development to make the defibrillator mobile. Pantridge & Geddes (1967) reported ten cases of out-of-hospital defibrillation, six of whom survived to leave hospital. These early reports

stimulated the study of out-of-hospital defibrillation in many other centres including Seattle (Cobb *et al.* 1971), Miami (Nagel *et al.* 1970) and Brighton (Mackintosh *et al.* 1978). Studies in dogs have confirmed that increasing duration of ventricular fibrillation is associated with increased energy requirements (Echt *et al.* 1988). As collection of data from studies of out-of-hospital resuscitation continued it became clear that the response time for delivery of the first defibrillation shock is a significant factor affecting survival (Weaver *et al.* 1986, 1988).

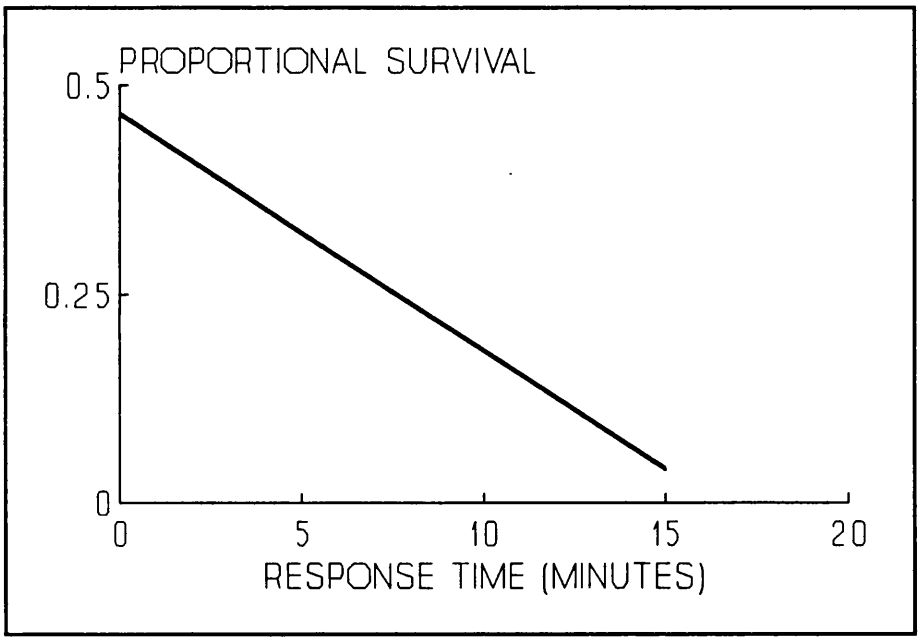

Figure 1.1: Linear regression line of probability of survival versus response time to defibrillation (modified from Weaver et al. 1986)

Even the most enthusiastic and efficient rapid-response system is likely to involve a delay of minutes and although the use of automatic advisory defibrillators by bystanders in public places, or by the spouses of patients at high risk (Hallstrom *et al.* 1984) or by transtelephonic control from hospital (Dalzell *et al.* 1988, 1991) may speed therapy delivery some delay is still involved. Additionally none of these approaches provide any protection from unwitnessed

cardiac arrest. Although these efforts may represent the best that can be done in patients who are not known to be at risk of cardiac arrest, it is not surprising that in the late 1960's thoughts turned to the development of an implantable defibrillator capable of protecting selected patients from ventricular fibrillation at all times.

The development of the Implantable Defibrillator:

The concept of automatically delivered defibrillation (Zacouto F 1953) predates the idea of an implanted defibrillator by nearly 15 years. However the construction of an implantable defibrillator only became practical with the increasing availability of electronic components in the 1960's.

In the late 1960's two separate groups addressed the problem of producing an implantable defibrillator. At the University of Missouri Schuder *et al.*(1970) performed the first implant of a self-contained defibrillator system in a dog. The components of this system were sealed in sterile rubber glove and consisted of a battery pack, DC-DC converter, capacitor, pulse generator and fibrillation detector. The capacitor output was discharged to two stainless steel electrodes implanted in the chest wall. Ventricular fibrillation was detected by examining the signal from a standard bipolar right ventricular electrode. The lack of R-waves for a period of 5 seconds would trigger the charging of the capacitor and shock delivery. Although this system was suitable only for short-term implantation and weighed 1037 grams it clearly demonstrated the feasibility of an implantable defibrillator.

At the same time Mirowski *et al.*(1970) were also working on the development of such a device. Their initial system was different from that of Schuder. It used a pressure sensing transducer to detect the loss of phasic pressure in the right ventricle during ventricular fibrillation. Shock delivery was between a right ventricular and subcutaneous electrode. In

1971 Mirowki's group reported defibrillation with the shock delivered by a single transvenous lead carrying two electrodes (Mirowski *et al.* 1971). They proceeded to demonstrate the feasibility of defibrillation in humans undergoing cardiac surgery using energies of 20 joules or less with an electrode in the right ventricle and a saline-soaked patch on the superior vena cava (Mirowski *et al.* 1973). Despite a critical reception from some authors (Lown & Axelrod 1972) work on a fully implantable automatic defibrillator for use in humans continued. Work accelerated after Mirowski and Mower teamed up with the Medrad company, which until then had specialised in the manufacture of angiographic injectors (Kastor 1989). By 1975 they had a device small enough to be implanted chronically in dogs. In 1978 the results of these chronic implantation studies were published (Mirowski *et al.* 1978). By this stage the weight had reduced to 250gm and a volume of 145ml and a purpose built implantable fibrillation induction device and defibrillation analyzer had been developed to assess the performance of the device. New battery technology had to be developed as no existing cell was entirely satisfactory (Horning & Rhoback 1982). By this time fibrillation detection was achieved by use of the probability density function (Chapter 2, Page 38) in place of haemodynamic sensing of right ventricular pressure.

This period of intensive development culminated in the first human implant of the ICD at the Johns Hopkins University School of Medicine in 1980 (Mirowski *et al.* 1980). Over the next five years 800 automatic implantable defibrillators were installed and FDA approval was obtained in 1985. The first European implant took place in 1982 at the Hospital Lariboisière, in Paris (Leclerq *et al.* 1983). The first implants in the United Kingdom took place at Guy's Hospital during 1984 (Sowton E *personal communication*, Holt *et al.* 1987).

In the twelve years since the first human implant the annual implant rate has increased almost exponentially such that over 25,000 devices have been implanted worldwide.

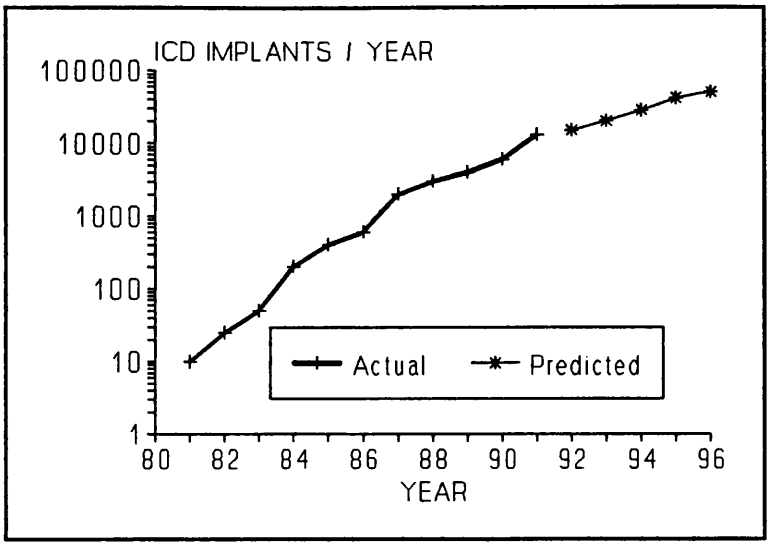

Figure 1.2: Implant rate of ICD's since 1981 and predicted implant rates for the 1990's (data from Cardiac Pacemakers Inc.). Implant rates have shown a steady exponential increase since 1981 although the rate of increase is predicted to slow somewhat

This explosion in implantation rates has occurred in parallel with the steady technical development of the device and the electrodes used with it.

ICD development since the first human implant:

The earliest implantable defibrillator, the CPI AID (Automatic Implantable Defibrillator) was a relatively simple device. It could detect the presence of ventricular fibrillation using the probability density function (PDF), a mathematical analysis of the proportion of time spent by the electrogram away from the baseline. The PDF alters markedly during ventricular fibrillation enabling its differentiation from sinus rhythm. The defibrillation shock was a truncated exponential capacitor discharge and was delivered between a coil electrode in the superior vena cava and a flexible cup electrode over the apex of the heart. This device was very effective in detecting and terminating ventricular fibrillation but it soon became clear

that in many patients the primary arrhythmia was haemodynamically unstable ventricular tachycardia rather than ventricular fibrillation and so the sensing circuitry was modified to include detection of heart rate. This required an additional bipolar right ventricular electrode for sensing purposes. The device remained relatively crude as the sensing and output parameters of the device had to be programmed at the time of manufacture and could not subsequently be altered. This was a major limitation in view of the variability in the rate of ventricular tachycardia which may occur spontaneously (Volosin *et al.* 1991), or in the presence of antiarrhythmic drugs (Paul *et al.* 1991). The Ventak 1550 and Ventak P models which had programmable detection rate were designed to alleviate this problem. They also incorporated programmable first shock energy and shock counters. The addition of bradycardia support pacing also alleviated a potential cause of morbidity and mortality after ICD therapy delivery as significant bradycardias may follow successful tachycardia termination (Jones *et al.* 1986) and in some high risk groups such as patients with dilated cardiomyopathy, may be responsible for a significant proportion of deaths (Luu *et al.* 1989).

Although it was clear that these second generation devices represented a major advance a number of additional features were clearly required before the implantable defibrillator could be thought of as an all round therapy for ventricular tachyarrhythmias.

The use of antitachycardia pacing for ventricular arrhythmias has a long history (Bennet & Pentecost 1971) but its application had been limited because of the occasional occurrence of tachycardia acceleration (Holley *et al.* 1986). The addition of antitachycardia pacing to the implantable defibrillator was a logical development with many potential advantages including increased patient tolerance, reduced battery consumption and possibly reduced requirement for antiarrhythmic drug therapy. By providing backup defibrillation in the event of tachycardia acceleration the implantable defibrillator radically improved the safety of ventricular antitachycardia pacing.

The second major development in third-generation defibrillators has been the availability of logging of therapy episodes. In its simplest form this involves recording the number of episodes of ventricular tachycardia or fibrillation detected, the therapies delivered by the device and the outcome of these therapies. Greater sophistication is available on a number of devices with storage of R-R intervals for multiple episodes and even of endocardial electrograms. These data can be recovered from the device at leisure and greatly facilitate programming and troubleshooting (Ellenbogen *et al.* 1991).

Third-generation defibrillators also offer increasing sophistication in the detection of tachycardias. Although all remain dependent on heart rate as the primary detection algorithm several devices incorporate regularity and sudden onset detection algorithms in an attempt to improve specificity of detection of ventricular arrhythmias versus atrial fibrillation and sinus tachycardia. Additionally they offer a multi-level response ("tiered therapy") depending on tachycardia rate to therapy with pacing alone, pacing therapy plus shock or shock only therapies.

When it became clear in the mid 1980's that there was a potential market for the implantable defibrillator a number of manufacturers commenced development work. As a result no less than six manufacturers are currently engaged in the evaluation of third-generation defibrillators. The features associated with the three generations of implantable defibrillator are shown in Table 1.1.

Table 1.1: Features of the three generations of ICD

Feature	Generation		
	1st	2nd	3rd
Defibrillation	+	+	+
Programmable shock output	-	+	+
Bradycardia support pacing	-	+	+
Antitachycardia pacing	-	-	+
Low energy cardioversion	-	-	+
Advanced data logging	-	-	+
Electrogram storage	-	-	+/-

These rapid technical developments have been associated with a steady reduction in weight and volume of the device (Figure 1.3). A significant further reduction in size and weight is likely to be achieved by reducing the maximum shock energy which the device can deliver, which enables a reduction in the size of both battery and capacitors. This in turn requires the development of lead systems capable of reliable defibrillation at lower shock energies. Technical developments in battery technology will also contribute to a reduction in size.

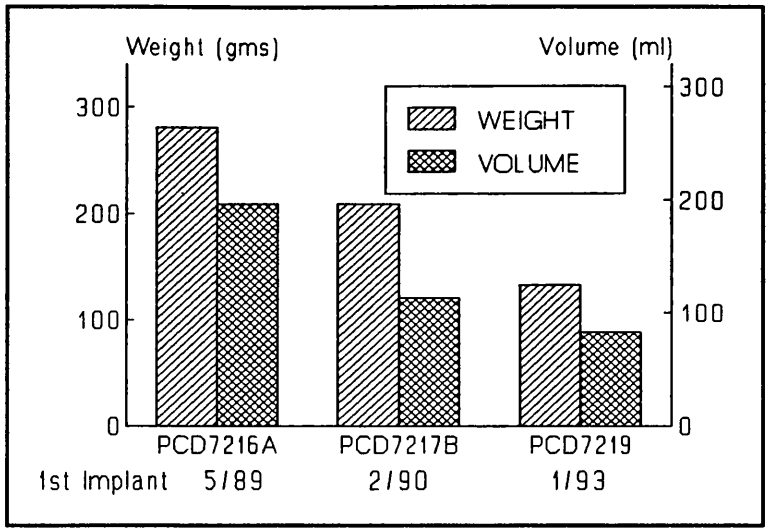

Figure 1.3: Progressive reduction in the weight and volume of the ICD. The Medtronic PCD 7217B is technically identical to the 7216A and yet a reduction of over 30% in weight and 40% in volume was possible

Development of Defibrillation Electrode Systems:

It was clear even from the early days of defibrillation that the size shape and location of defibrillation electrodes was of considerable importance (MacLean & van Tyn 1961). This is of particular relevance with an implantable defibrillator where defibrillation thresholds are required to be as low as possible. In the first human implants a spring electrode was positioned in the superior vena cava and a cup electrode was placed over the apex of the right ventricle (Mirowski *et al.* 1980). Subsequently it became clear that lower defibrillation thresholds could be obtained by using two epicardial patch electrodes with a higher surface area (Troup *et al.* 1985). This became the standard for subsequent implants with the addition of a third patch electrode if necessary. Over 90% of all implantable defibrillators so far implanted have used a system of this type.

A major drawback of epicardial patch electrode systems was the necessity for some form of thoracotomy and epicardial pacing and sensing electrodes were already known to offer poor performance when compared with endocardial systems (Oldershaw *et al.* 1982). For this reason interest in the possible use of a transvenous electrode system remained high and development continued. The first such system developed was the CPI Endotak™ which was initially implanted in 1986. This lead has a pace-sense electrode at its tip and two defibrillation electrodes on its body and may be used alone or in conjunction with a subcutaneous patch electrode (See page 48, figure 2.13). The initial version of this lead suffered a number of a lead fractures and was replaced by a modified version in 1989. The Medtronic Transvene™ (previously called NTL) system was introduced in 1989. This is a two lead system. A right ventricular lead carries two pace sense electrodes and a defibrillation electrode whilst a superior vena cava lead carries a single defibrillation electrode. A similar system has been developed by Telectronics but using an atrial "J" electrode in place of a free floating superior vena cava electrode. Other manufacturers are also conducting pilot studies with transvenous electrode systems.

Thus the last decade has been one of intense technical development in devices and electrode systems in parallel with the dramatic increase in the number of devices implanted.

Development of ICD Implantation in the United Kingdom:

As with so many aspects of medical care there has been no central strategy for the introduction and evaluation of ICD therapy within the United Kingdom. Following the first implant at Guy's in 1984 implantation proceeded very slowly with the first implant at St. George's in July 1986. By January 1990 49 devices had been implanted at 10 centres (Griffith *et al.* 1990b) and the number of implants and implanting centres have continued to rise

steadily. The current number of implants is thought to lie between 360 and 380 (Nathan AW *personal communication*) although no published data are available.

INTRODUCTION

PART II: ICD USE - CURRENT ISSUES

Does the ICD improve survival?

Although the implantable defibrillator has been available for 12 years and over 25,000 have been implanted worldwide this question has yet to be answered by a rigorously conducted prospective controlled trial. A number of such trials are now in progress and should provide a definitive answer to this question in the next few years. In the absence of these data a variety of comparisons of survival data have been performed to try to assess whether the implantable defibrillator reduces mortality.

Hypothetical Survival Studies:

The simplest approach is to use ICD recipients as their own controls and to decide when they would have died had they not received their ICD, and to compare that with their actual survival. This relies on the assumption that the first occasion on which the defibrillator delivers a shock for a ventricular arrhythmia the arrhythmia would otherwise have been fatal. The earliest published survival studies of the ICD were of this type. Mirowski *et al.*(1983) reported survival in 52 early ICD recipients (Figure 1.4). Figure 1.5 shows the results of a another study of this type in 22 ICD recipients (Gabry *et al.* 1987).

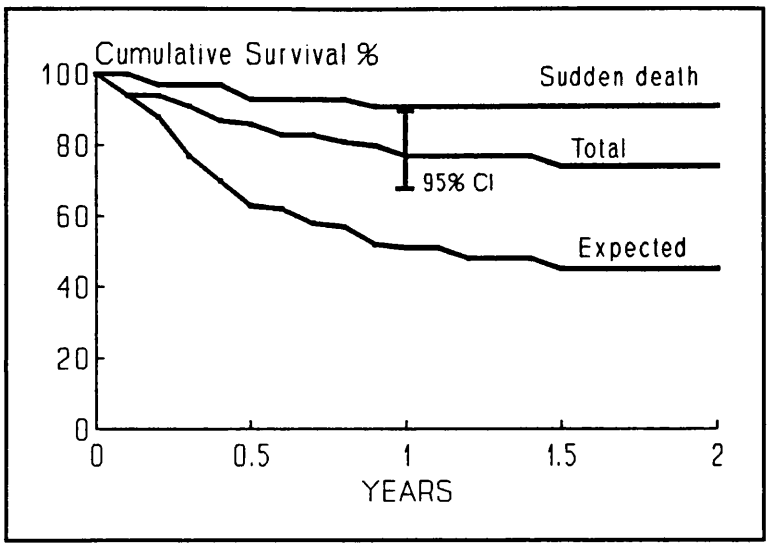

Figure 1.4: Total survival and survival free of sudden death in 52 recipients of the ICD compared with hypothetical survival (Expected) assuming the first appropriate ICD shock is for an arrhythmia which would otherwise have proved fatal. The 95% confidence interval for survival at one year is shown (95% CI). Data from Mirowski et al.(1983)

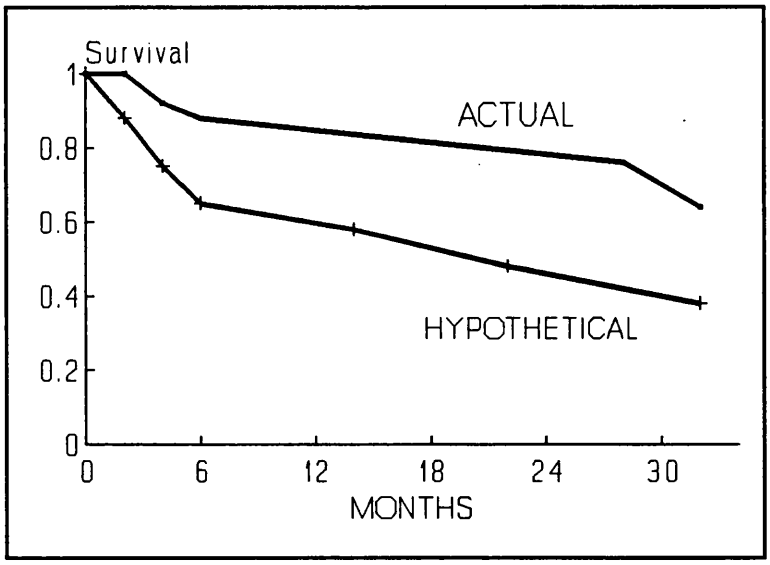

Figure 1.5: Actual compared with hypothetical survival for 22 ICD recipients (Gabry et al. 1987)

There are many potential flaws in this type of comparison. It is clear that all episodes of recurrent ventricular arrhythmia are not invariably fatal. With the early generation ICD's used in these studies there was no facility to store cycle lengths or electrograms of the arrhythmia precipitating the therapy and therefore precise identification of appropriate and inappropriate therapies was difficult. The association or absence of symptoms preceding delivery of therapy is a poor guide to the presence or absence of a serious arrhythmia (Grimm *et al.* 1992). This type of study tends to overestimate the benefit of ICD use.

Even if such a study was to be performed using only modern ICD's with sophisticated data logging facilities there are problems with interpretation. For example the occurrence of an attack of stable ventricular tachycardia, readily terminated by antitachycardia pacing, would not necessarily have been benign in a patient without an ICD. The ventricular tachycardia could have been prolonged, resulting in hypotension, myocardial ischaemia and acceleration into ventricular fibrillation. Conversely, a patient with a rapid unstable ventricular tachycardia would not necessarily have died in the absence of ICD treatment.

Historical Comparison:

In the absence of controlled studies of survival after ICD use the commonest comparison has been between groups of patients treated before and after the availability of the implantable defibrillator. Nisam *et al.*(1991) compared survival data for 258 patients who received antiarrhythmic drug therapy guided by electrophysiological testing (Waller *et al.* 1987) with that of 270 implantable defibrillator patients (Winkle *et al.* 1989a). The patients treated with antiarrhythmic drug therapy were divided into three groups on the basis of their response at electrophysiologic study. Group 1 were patients whose arrhythmia was rendered noninducible by the drug therapy. Group 2 still had an inducible arrhythmia but this had a cycle length >100ms slower than the arrhythmia induced at initial study and this arrhythmia was not

associated with haemodynamically significant symptoms. Group 3 still had an inducible arrhythmia with no evidence of slowing attributable to antiarrhythmic drug therapy. The majority of these patients received empiric amiodarone therapy. Figure 1.6 shows the survival data from these two studies.

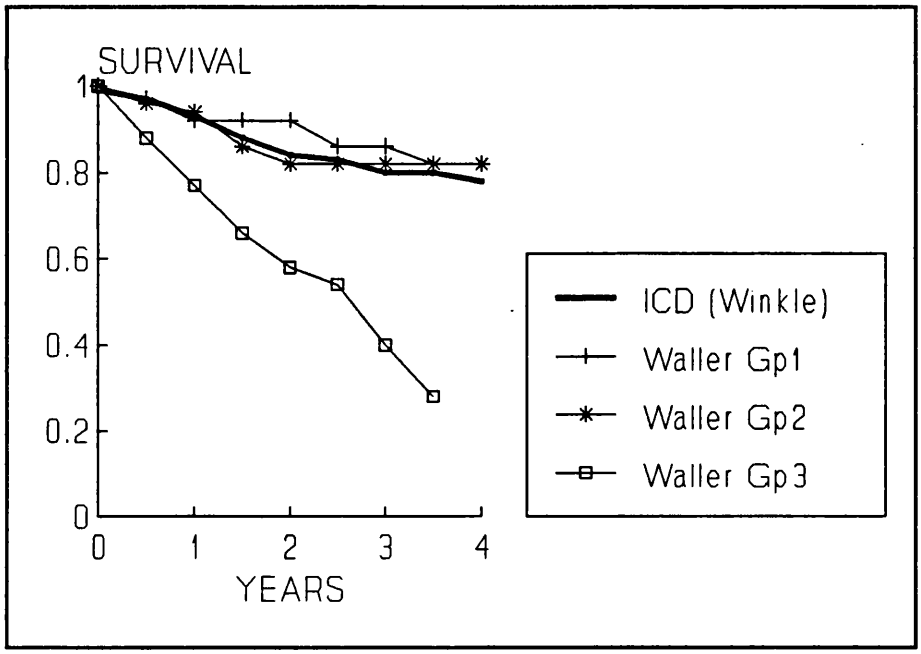

Figure 1.6: Survival with ICD use in drug resistant patients (ICD) compared with patients with ventricular arrhythmia suppressed by antiarrhythmic drug therapy (Waller Gp1), slowed by >100ms (Waller Gp2), or unaffected by antiarrhythmic drug therapy (Waller Gp3)

Because the patients in Winkle's study had been resistant to 3.4 (+/- 1.9) antiarrhythmic drugs at electrophysiological testing prior to implantable defibrillator insertion their survival might be expected to be similar to that of Waller's Group 3 patients. However the ICD patients clearly fared much better with survival similar to Waller's drug-responsive patients. A number of such empiric historical comparisons have been made all of which suggest some improvement in survival related to the use of the implantable defibrillator. However there

are potential flaws in such studies. The series are not contemporaneous and the mean ejection fraction in the ICD recipients was 34% whereas that in Waller's Group 3 patients was 25%. This confounding variable could explain some of the observed difference in survival and other less obvious factors associated with differences in measurement and management at different institutions could also account for some of the observed differences in survival.

A number of historical comparisons have been performed within the same institution to try to minimise this source of error. Fogoros and colleagues (1987) studied a cohort of 78 consecutive patients with symptomatic, sustained, drug-refractory ventricular arrhythmias. Prior to February 1985 patients were treated with the implantable defibrillator and amiodarone if they presented with syncope and amiodarone alone if they did not. Due to difficulties with obtaining defibrillators patients presenting after February 1985 received amiodarone alone however they presented. Figure 1.7 shows the comparative survival for these groups. The survival in the amiodarone treated patients presenting with syncope was significantly worse than in the ICD treated group ($p<0.003$) or the patients without syncope who were treated with amiodarone ($p<0.03$). Although the groups were not deliberately matched the values for confounding variables such as ejection fraction and underlying disease status were similar within the groups.

Another historical study (Newman *et al.* 1992) compared the actuarial survival of 60 ICD recipients with 120 medically treated control patients. The controls were carefully matched for age, left ventricular ejection fraction, arrhythmia at presentation, underlying heart disease and drug therapy. The comparative survival of the two groups is shown in Figure 1.8.

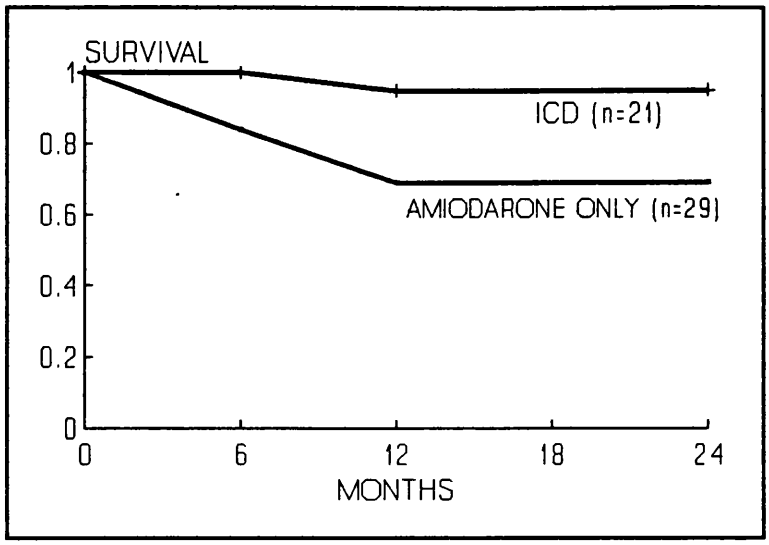

Figure 1.7: Comparison of survival with the ICD versus amiodarone for patients presenting with syncope and ventricular arrhythmias (Fogoros et al. 1987)

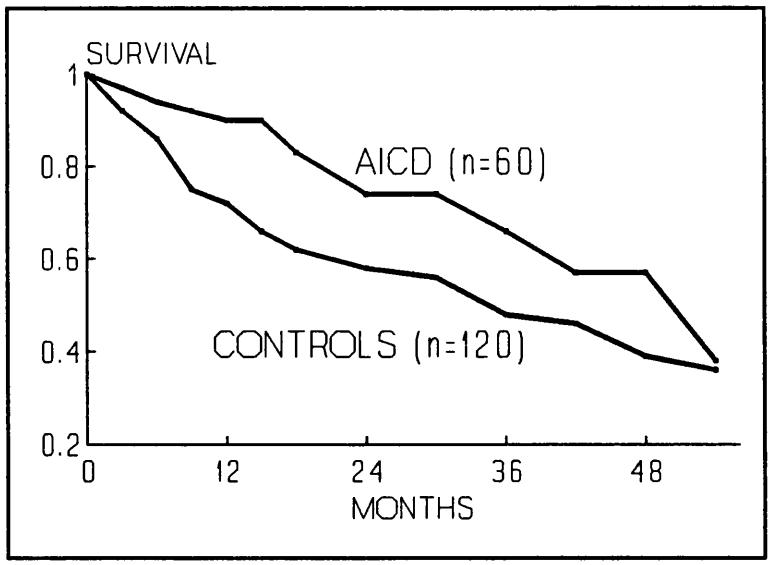

Figure 1.8: Comparative survival of matched ICD recipients and medically treated controls

The authors compared the survival in the two groups using the Cox proportional hazard model and this showed a significant difference in survival over the 60 months of the study

($p<0.05$). However the progressive convergence of the survival curves at the end of the period is concerning, suggesting as it does that the initial survival advantage conferred by the ICD might be lost with time. However confidence limits for the survival curves at this point are wide due to the small number of patients with this duration of follow-up.

All three of these historical comparisons suggest that the ICD improves survival when compared with conventional antiarrhythmic drug therapy. However because of the inherent flaws in nonprospective, nonrandomized studies caution must be exercised in interpreting these data.

Who should receive an ICD?

The primary indication for implantation of an ICD is the prevention of sudden death due to ventricular arrhythmias in patients who are known to be at high risk of such events. Unfortunately, the use of the ICD is not without risk and it is important that these risks are outweighed by the benefits of its use. In the last year three major national and international professional bodies with an interest in cardiology have issued guidelines for ICD implantation. The main features of these guidelines are summarized in Tables 1.2 & 1.3. There is considerable difference in emphasis, particularly between the European and American institutions, with the European guidelines being softer and less didactic. A large number of studies of possible additional indications for the ICD are under investigation and these will be discussed in Chapter 7. Although there is some consensus over the general type of patient who should be receiving an ICD there remain a number of areas of controversy such as the benefit of the ICD in patients with poor ventricular function and whether delivery of an ICD therapy is by itself a negative prognostic indicator.

Table 1.2: Recommendations for ICD implantation in the USA (Class I - ICD indicated, Class II - indication unclear, Class III - ICD not indicated)

ORGANISATION	CATEGORIES			ICD ?
NASPE POLICY CONFERENCE (Lehman MH & Saksena S. 1991)	Class I	-	VT/VF in a patient where EPS or Holter recording cannot be used to predict efficacy of therapies	+
		-	recurrent VT/VF despite EPS/Holter guided therapy	
		-	spontaneous VT/VF where drug therapy is limited by compliance/tolerance	
		-	persistent inducibility of VT/VF despite best available drug therapy/surgery/catheter ablation	
	Class II	-	Syncope of unknown aetiology in a patient with VT/VF at EPS where drug therapy is limited by efficacy,compliance or intolerance	+/-
	Class III	-	VT/VF due to ischaemia/infarction or toxic/metabolic causes	-
		-	recurrent syncope without ventricular arrhythmias	
		-	incessant VT/VF	
		-	VF secondary to AF in the Wolff-Parkinson-White syndrome	
ACC/AHA TASK FORCE (Dreifus *et al.* 1991)	Class I	-	Haemodynamically significant VT/VF where EPS or Holter recording cannot be used to predict efficacy of therapy	+
		-	Haemodynamically significant VT/VF where no drug effective or tolerated	
		-	VT/VF remains inducible at EPS despite drugs/catheter ablation/surgery	
	Class II	-	Haemodynamically significant VT/VF where drug efficacy testing is possible	+/-
		-	Recurrent syncope of undetermined origin in a patient with VT/VF at EPS and in whom no drug is effective or tolerated	
	Class III	-	Recurrent syncope of undetermined cause in a patient without inducible tachyarrhythmias	-
		-	Arrhythmias other than haemodynamically significant VT/VF	
		-	Incessant VT/VF	

NASPE = North American Society of Pacing and Electrophysiology
ACC = American College of Cardiology
AHA = American Heart Association
VT = Ventricular tachycardia
VF = Ventricular fibrillation
EPS = Electrophysiological study

Table 1.3: European Society of Cardiology Guidelines for ICD implantation in the Europe: (Task Force 1992)

ICD USE GUIDELINES REGARDLESS OF AETIOLOGY OF PRIMARY DISEASE	- If EPS reproducibly induces VT/VF, suppressive drug therapy should be sought - If spontaneous episodes recur or sustained VT/VF remains inducible on drugs, or if drugs are not tolerated and surgery is inappropriate an ICD should be implanted - If EPS is unreliable for drug assessment, an ICD may be used on an individual basis although this indication has yet to be clarified - If EPS does not provoke a sustained ventricular arrhythmia and the presenting arrhythmia is judged to be due to a self limiting event (i.e. infarction, toxic,metabolic) no further antiarrhythmic action may be necessary. If the arrhythmia can be shown to be due to ischaemia then revascularisation may be the preferred option. - If EPS provokes VT/VF and drug therapy is ineffective or not tolerated treatment options include ICD implantation, less easily tested antiarrhythmic drugs (ß-blockers, amiodarone), antiarrhythmic surgery, ablation and treatment of the primary disease process	
ICD USE GUIDELINES DEPENDENT UPON AETIOLOGY OF PRIMARY DISEASE	Sustained VT >48 hours post MI	If EPS directed drug therapy fails, surgery, transplantation and the ICD are alternatives
	VF complicating acute <48 hours post MI	ICD not indicated
	Out-of hospital cardiac arrest secondary to non Q-wave MI	Investigation of coronary anatomy ± revascularisation
	Cardiac arrest without infarction but with coronary disease	Investigation of coronary anatomy. ICD rarely indicated
	Hypertrophic cardiomyopathy	ICD may have a role if high risk patients can be identified
	Dilated cardiomyopathy with ventricular arrhythmias	ICD may have a role if high risk patients can be identified - possibly as a bridge to transplant
	Congenital long QT syndromes	ß-blockers, pacing, stellate ganglionectomy and the ICD may all have a role to play
	Mitral valve prolapse with arrhythmias	ICD may be indicated in individual patients
	WPW with atrial fibrillation	ICD not indicated. Surgical/catheter ablation is the treatment of choice

VT = Ventricular tachycardia VF = Ventricular fibrillation EPS = Electrophysiological study WPW = Wolff-Parkinson-White syndrome

The current status of transvenous electrode systems:

The potential advantages of transvenous lead systems compared with epicardial systems are considerable. Avoidance of a thoracotomy with its associated morbidity and mortality, and the potential for prepectoral implantation of the defibrillator which would allow the use of shorter leads are amongst these advantages. Over the last five years several manufacturers have been conducting studies on the chronic performance of their endocardial electrodes and a general review of the merits of the two approaches to lead implantation is now possible.

Cost issues and ICD use:

The average cost of an ICD generator and leads is approximately £15,000 and there is no doubt that the ICD is perceived as an expensive therapy (Campbell RWF 1990) and that this has limited its use in the United Kingdom. However, more detailed consideration of the cost-efficacy of the device is required to assess its true position in relation to other therapies. A detailed consideration of the cost-efficacy of the device is provided in Chapter 7 of this thesis.

Driving and the ICD:

One of the major drawbacks for recipients of the ICD in the United Kingdom is that they are currently not allowed to drive (Gold & Oliver 1990). This regulation is based on understandable fear of recurrent cardiac arrest in these patients. It contrasts strongly with the situation in the United States where no states have specific restrictions on driving by ICD recipients and only 52% of states have restrictions on patients with syncopal arrhythmic episodes (Strickberger *et al.* 1991). Most physicians in the United States recommend only a

limited period of abstinence from driving for their patients (DiCarlo *et al.* 1992). The issue of driving with an ICD is considered in more detail in Chapter 6 of this thesis.

AIMS OF THIS THESIS:

- To study the pre-operative factors which predict the success or failure of implantation of the ICD using transvenous electrodes

- To evaluate the outcome of patients treated with the implantable cardioverter defibrillator and the impact of various risk factors on this outcome

- To assess the efficacy and long-term stability of transvenous defibrillation electrode systems

- To measure the impact of arrhythmias on the ability to perform psychomotor tasks and the implications of these data for the lifestyle of ICD recipients and the current regulations concerning driving with an ICD

- To develop a simple model of the cost-efficacy of implantable defibrillator use and to apply this model to current and future uses of the ICD.

** ** ** ** **

CHAPTER 2:

EQUIPMENT AND PATIENTS

Development of ICD implantation at St. George's Hospital:

This study reports our experience with the first 48 patients in whom ICD implantation was attempted at St. George's Hospital London. Successful ICD implantation was achieved in 47 of these patients. The first implant was performed during July 1986 and the last implant in this study took place in September 1992. The distribution of the 46 implants occurring between 1988 and 1992 is shown in Figure 2.1.

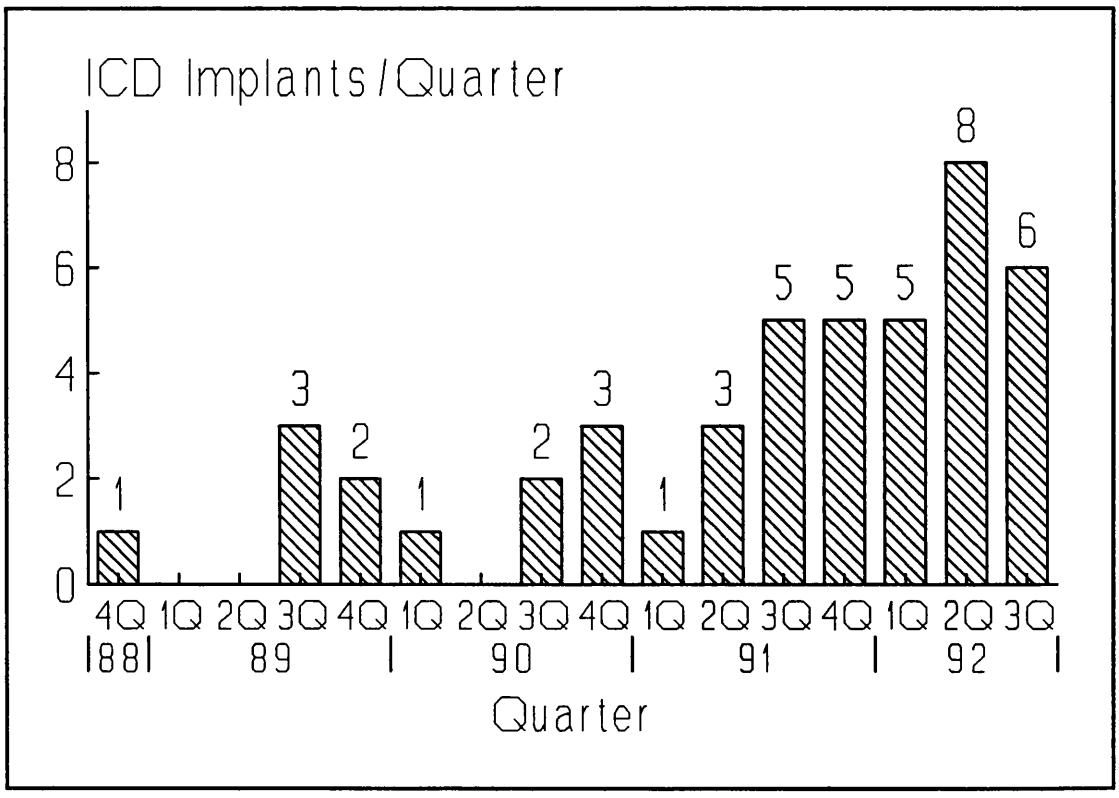

Figure 2.1 Quarterly implant figures for ICD's at St. George's Hospital 1988-1992

General Features of ICD Systems Used in this Study:

The pattern of use of ICD systems has been influenced by their availability and the features which each system offered. The basic concept of the ICD is very simple and is summarized in Figure 2.2

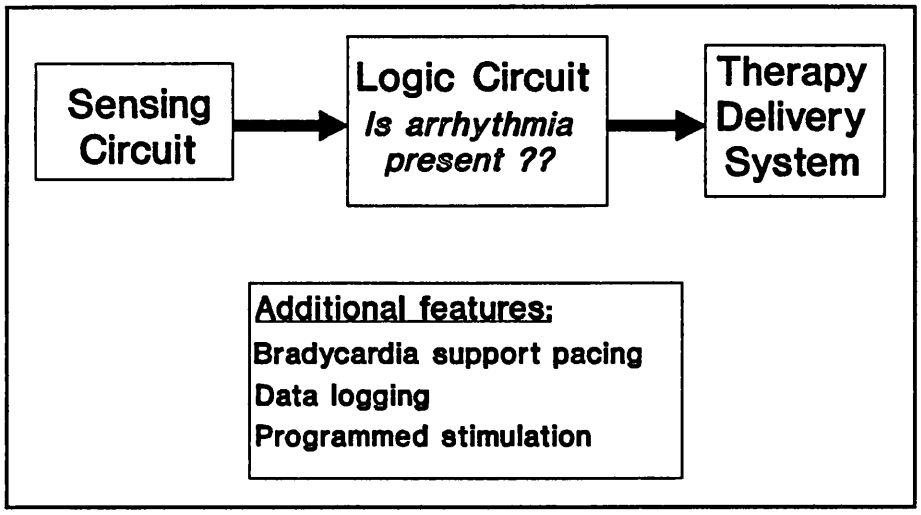

Figure 2.2: The basic concept of the ICD

Despite the simplicity of the concept there is considerable diversity in the means by which it is realized in different ICD generators.

Manufacturers and Trademarks:

ICDs and lead systems from four manufacturers (Medtronic, CPI, Telectronics and Ventritex) have been used in these studies. Details of these manufacturers and their trademarks are listed in Appendix D.

Sensing and Tachycardia Detection:

All currently available ICD generators base their tachycardia detection on analysis of a bipolar electrogram derived from either a dedicated bipolar pacing electrode system or from a pacing electrode and a shock electrode. All systems rely primarily on detection of heart rate and this involves identification of the R waves on the incoming signal. The sensing circuitry of the ICD must be capable of detecting the low amplitude signals which may occur during ventricular fibrillation without oversensing during sinus rhythm. To overcome this potential problem newer models of the ICD include some form of time-dependent automatic sensitivity control. That used in the Medtronic PCD is illustrated in Figure 2.3.

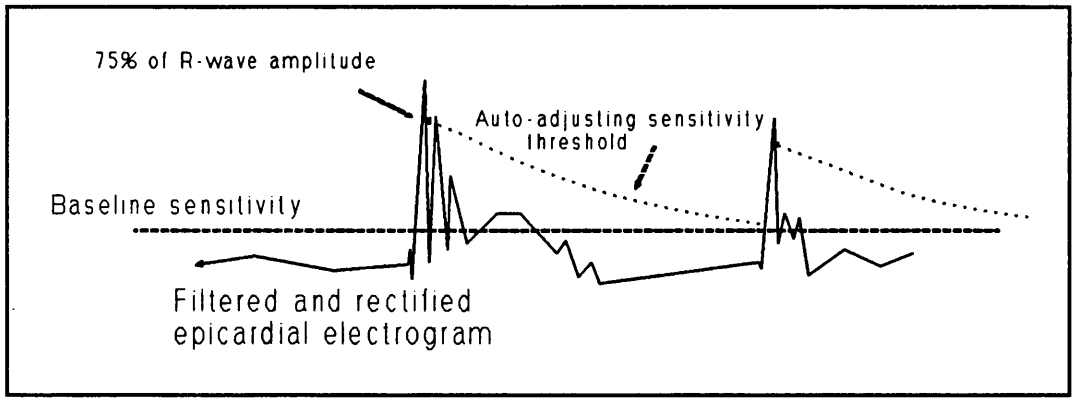

Figure 2.3: The automatic sensitivity adjustment system of the Medtronic PCD. After each sensed R-wave sensitivity is reduced to 75% of the R-wave amplitude and decays exponentially back to baseline sensitivity

With the exception of the Guardian 4202 all devices used in this study use some form of automatic gain to enhance arrhythmia detection.

The R-R intervals produced by the sensing circuitry may be processed in a variety of ways by the logic circuit to decide whether an arrhythmia is present. The simplest approach is to use a rigid rate threshold and to require that a certain number of consecutive R-R intervals

should cross this threshold (Figure 2.4). This type of algorithm is used in the Medtronic PCD for detection of ventricular tachycardia.

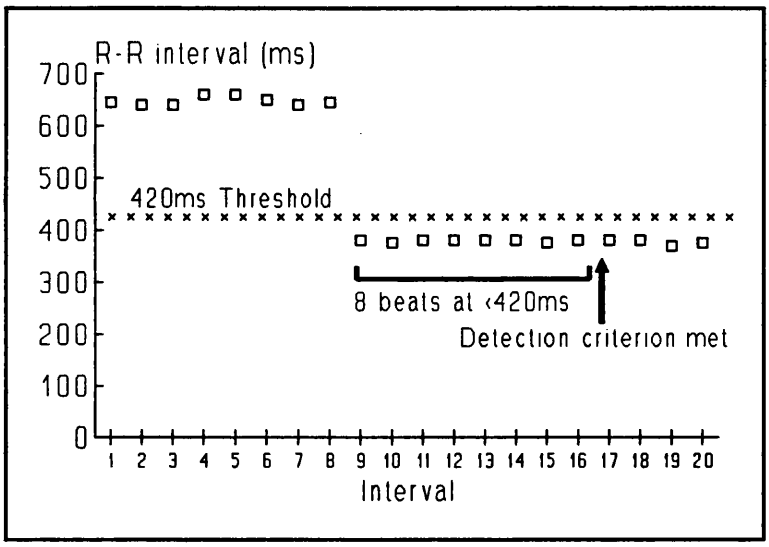

Figure 2.4: Operation of a rigid rate threshold requiring 8 beats faster than 420ms for detection of ventricular tachycardia. All 8 beats must cross the 420ms threshold or the detection criterion is not met

Whilst the rigid rate threshold is satisfactory for detection of arrhythmias such as ventricular tachycardia where there is unlikely to be any loss of sensing it is not satisfactory for ventricular fibrillation. To avoid failure to sense ventricular fibrillation due to undersensing of low amplitude electrograms all devices use a rate threshold which has to be satisfied by only a proportion (usually between 70% and 80%) of R-R intervals (Figure 2.5). This type of threshold is used in CPI and Telectronics devices for ventricular tachycardia detection too but this type of algorithm may be more easily satisfied by atrial fibrillation than the more rigid algorithm used in the Medtronic PCD giving rise to an increased risk of inappropriate therapy delivery.

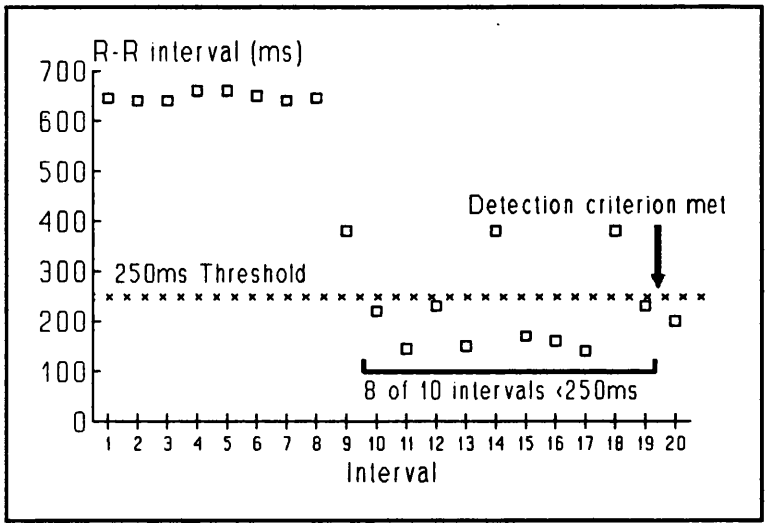

Figure 2.5: Proportional rate threshold. Provided ≥80% of R-R intervals are less than 250ms the detection criterion is met

Detection based on heart rate alone has very high sensitivity but its specificity is relatively poor as erroneous satisfaction of rate threshold can occur as a result of sinus tachycardia or atrial fibrillation. In published ICD series atrial fibrillation has resulted in inappropriate therapy delivery in between 4 and 8 percent of patients (Manolis *et al.* 1989, Fromer *et al.* 1992). To try to reduce the scale of this problem many of the more sophisticated ICD's now offer a programmable rate stability function. The precise way in which rate stability is computed in different devices varies but Figure 2.6 illustrates the system used in the Ventak PRx.

Overlap of maximum sinus heart rate with ventricular tachycardia rate occurs in 11% of patients with drug resistant ventricular tachycardia (Paul *et al.* 1991). To try to reduce the incidence of inappropriate detection caused by sinus tachycardia some devices offer a programmable sudden onset detector. This works on the assumption that sinus tachycardia is associated with a gradual increase in heart rate whilst pathological tachycardias are

associated with a sudden change in rate. The precise way in which the onset criterion is calculated varies between devices but the general principle is illustrated in Figure 2.7.

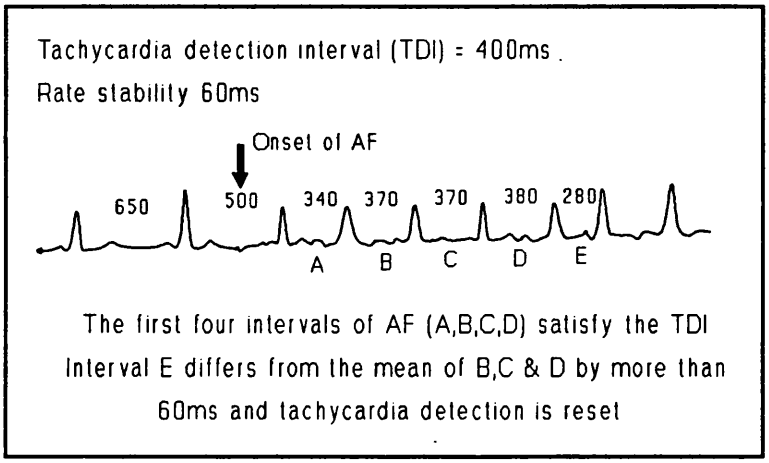

Figure 2.6: Use of a rate stability criterion to minimise inappropriate detection caused by atrial fibrillation

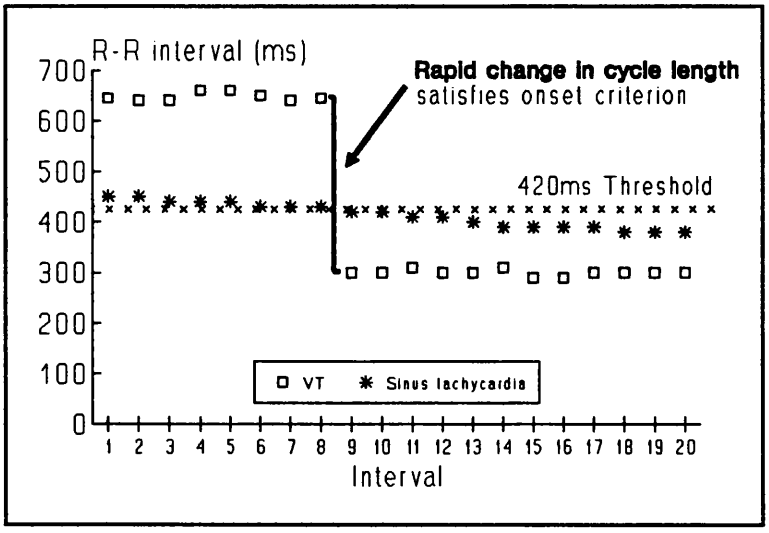

Figure 2.7: Use of the onset criterion to minimise inappropriate detection caused by sinus tachycardia

Although rate stability and onset criteria are now widely available their use has been limited because time-consuming evaluation is needed to minimise the risk of reduced sensitivity of tachycardia detection when these algorithms are enabled. It is the very high sensitivity of rate-only detection criteria which are thought to be responsible in part for the excellent survival figures from the early ICD studies. One approach to minimising the risk of loss of sensitivity has been to use a prolonged high rate criterion, whereby any tachycardia which persists for more than a programmed period receives therapies, whether or not the stability or sudden onset criteria have been satisfied. These attempts to improve the specificity of arrhythmia detection are based on ventricular sensing alone and serve to highlight the need for a second rate-independent sensor for arrhythmia detection.

Multizone Tachycardia Detection Algorithms:

Devices with this feature allow you to programme different therapeutic responses to tachycardias of different rates. This facility has become known as "tiered therapy". For example, after detection of a relatively slow ventricular tachycardia the ICD could be programmed to receive antitachycardia pacing initially followed by low and then high energy cardioversion shocks if the pacing therapies were ineffective. If a more rapid ventricular tachycardia or ventricular fibrillation is detected the ICD would proceed immediately to high energy shock therapies. Currently available devices offer between two and four detection zones with programmable boundaries and therapy delivery.

The Probability Density Function:

This rate independent detection algorithm identifies a percentage reduction in the time spent by the intracardiac electrogram on or very near to the baseline (Figure 2.8).

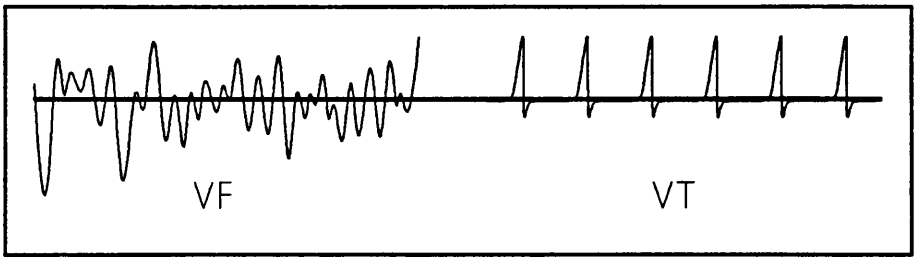

Figure 2.8: The probability density function measures time spent by the electrogram away from the baseline. In ventricular fibrillation (VF) the electrogram spends more time away from the baseline than during ventricular tachycardia (VT)

This is a useful criterion for the detection of ventricular fibrillation but is less sensitive for ventricular tachycardia (Lin *et al.* 1988) and it is therefore of limited use as a primary arrhythmia detector in devices designed to treat ventricular tachycardia as well as fibrillation. More recent research has also suggested that the function may be satisfied in some patients by sinus tachycardia (Toivonen *et al.* 1992).

Therapy Choices:

Shock therapies:

The primary function of all ICD generators is the delivery of a high energy (up to 40 joules) defibrillation shock in response to triggering of their tachycardia detection circuitry. All the devices used in this study allow the energy of the first shock to be programmed to a lower level and the devices with multizone tachycardia detection algorithms allow programming of low energy (<5 joules) cardioversion therapies. The standard shock morphology is the monophasic truncated exponential capacitor discharge although the Ventritex Cadence and CPI Ventak P2 offer the programmable alternative of biphasic shocks

which are thought to offer lower defibrillation thresholds (Flaker *et al.* 1989, Winkle *et al.* 1989b).

Although energy levels in joules are referred to throughout this thesis it is important to remember that the means by which this delivered energy is calculated varies between manufacturers. For CPI a constant energy circuit is used which adjusts the shock pulse duration to ensure constant energy delivery in spite of varying shock pathway impedance. Medtronic and Telectronics deliver a standard voltage and pulse width and the energy delivered is based on a notional impedance value. In the Ventritex Cadence pulse width is programmed manually on the basis of observed shock pathway impedance. Depending on the device and the arrhythmia detected shock therapies may be committed (once charging of the capacitors has commenced the shock will be delivered even if the arrhythmia terminates) or noncommitted (termination of the arrhythmia at any time prior to the shock will result in abortion of therapy delivery). If the initial shock therapy is ineffective all devices proceed to deliver between 3 and 6 further shocks in an effort to terminate the arrhythmia.

Pacing therapies:

Many of the ICD's used in this study are third-generation devices capable of delivering antitachycardia pacing therapies for ventricular tachycardia. A variety of pacing algorithms are available on the different devices and the programmable features include the number of pacing therapies delivered, the number of beats in each therapy, coupling interval of the therapy to the last beat of tachycardia, cycle length of the pacing therapy (as a percentage of tachycardia cycle length), and the decrement of pacing cycle length within and between each pacing therapy. In some devices (i.e. the Ventak PRx and Ventritex Cadence) a time limit for antitachycardia pacing therapies can be programmed after which the device will proceed to shock therapy even if all programmed antitachycardia pacing therapies have

not yet been delivered. All devices have some means of detecting tachycardia acceleration causing them to switch to more aggressive therapy delivery.

Data logging and electrogram storage:

One of the major advances in implantable defibrillators over the last 5 years has been the development of data logging, where the device stores information about its own performance, the number of episodes of arrhythmia detected, the therapies delivered and whether they were successful. Additionally the devices can store cycle lengths, electrograms or in some cases both for a limited number of arrhythmia episodes.

The standard data logs from a Medtronic PCD defibrillator are shown in Figure 2.9. These report how many episodes of arrhythmia occurred, how they were treated and whether the treatment was successful. It is important to remember however that the classification of arrhythmias by the device is based on its programmed detection criteria. Thus if an episode of atrial fibrillation succeeds in fulfilling the criteria for ventricular tachycardia detection the device will log it as an episode of ventricular tachycardia. Cycle length and electrogram recordings can help to resolve this dilemma by making the irregularity of the arrhythmia obvious (Figure 2.10).

Figure 2.9: Data logs from a Medtronic PCD defibrillator

```
MEDTRONIC 9420PCD TELETRACE RECEIVER
SOFTWARE REVISION: 9420PCD-002
PCD MODEL 7216
TRANSMITTER ID: 00000225

TELEMETRY
---------

PERM TELEMETRY ENABLE              OFF
TELEMETRY TYPE                    MRKR

DATA
----

PCD STATUS:
 MEMORY RETENTION                   OK
 CHARGE CIRCUIT                     OK
 LAST CHARGE TIME                 1.30 SEC
 CIRCUITRY BATTERY                3.05 V
 CHARGING BATTERY                 6.39 V

VT ONSET COUNTER                     0

VT EPISODE AND THERAPY DATA:
 EPISODE COUNT                      41
 VT THERAPY #1 SUCCESS COUNT        36
 VT THERAPY #2 SUCCESS COUNT         1
 VT THERAPY #3 SUCCESS COUNT         0
 VT THERAPY #4 SUCCESS COUNT         0
 # OF VT'S PCD INEFFECTIVE          4
 PCD EFFICACIOUS ON LAST VT        YES
 LAST THERAPY USED                  #1
 #SEQ IN LAST PACE THERAPY          1
 R-R AVG FOR LAST PACE THRPY      380 MS

VF EPISODE AND THERAPY DATA:
 EPISODE COUNT                      44
 VF THERAPY #1 SUCCESS COUNT        42
 VF THERAPY #2 SUCCESS COUNT         2
 VF THERAPY #3 SUCCESS COUNT         0
 VF THERAPY #4 SUCCESS COUNT         0
 PCD EFFICACIOUS ON LAST VF        YES
 LAST THERAPY USED                  #1
- - - - - - - - - - - - - - - - - - - -

MEDTRONIC 9420PCD TELETRACE RECEIVER
SOFTWARE REVISION: 9420PCD-002
PCD MODEL 7216
TRANSMITTER ID: 00000225

LAST EPISODE DETECTION SEQUENCE
  -19. R-R INTERVAL- 410 MS
  -18. R-R INTERVAL- 360 MS
  -17. R-R INTERVAL- 380 MS
  -16. R-R INTERVAL- 400 MS
  -15. R-R INTERVAL- 340 MS
  -14. R-R INTERVAL- 390 MS
  -13. R-R INTERVAL- 380 MS
  -12. R-R INTERVAL- 370 MS
  -11. R-R INTERVAL- 370 MS
  -10. R-R INTERVAL- 380 MS
   -9. R-R INTERVAL- 370 MS
   -8. R-R INTERVAL- 380 MS
   -7. R-R INTERVAL- 370 MS
   -6. R-R INTERVAL- 380 MS
   -5. R-R INTERVAL- 380 MS
   -4. R-R INTERVAL- 380 MS
   -3. R-R INTERVAL- 380 MS
   -2. R-R INTERVAL- 380 MS
   -1. R-R INTERVAL- 370 MS
   -0. R-R INTERVAL- 380 MS
   -0. VT DETECTED

EVENTS AFTER LAST THERAPY:
   +0. VT THERAPY #1 DELIVERED
   +1. R-R INTERVAL- 1000MS
   +2. R-R INTERVAL- 670MS
   +3. R-R INTERVAL- 1060MS
   +4. R-R INTERVAL- 1050MS
   +5. R-R INTERVAL- 1060MS
   +6. R-R INTERVAL- 1040MS
   +7. R-R INTERVAL- 1040MS
   +8. R-R INTERVAL- 1050MS
   +9. R-R INTERVAL- 1040MS
  +10. R-R INTERVAL- 1070MS
  +10. THERAPY WAS SUCCESSFUL
```

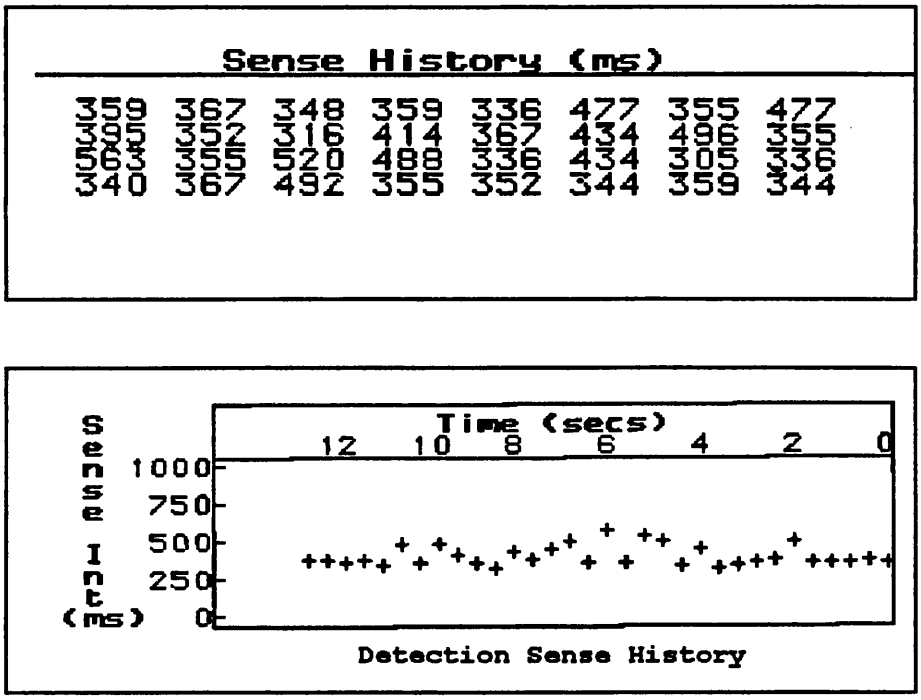

Figure 2.10: Detection cycle length table and cycle length plot for an episode of arrhythmia in a patient with a Telectronics Guardian 4210 defibrillator. The episode was classified as ventricular tachycardia and resulted in delivery of a shock therapy. Examination of the cycle lengths clearly reveals marked irregularity and this observation is confirmed by the cycle length plot. The patient was admitted as an emergency after the delivery of over 30 defibrillator shocks in two hours and was found to be in atrial fibrillation

Cycle length data is of particular use when reprogramming of the defibrillator is required as detection parameters are programmed by cycle length. However electrograms may contain additional information particularly when a lead break has occurred (Figure 2.11) or when far field atrial signals are visible. With this additional information reliable classification of most out-of-hospital arrhythmia episodes is possible.

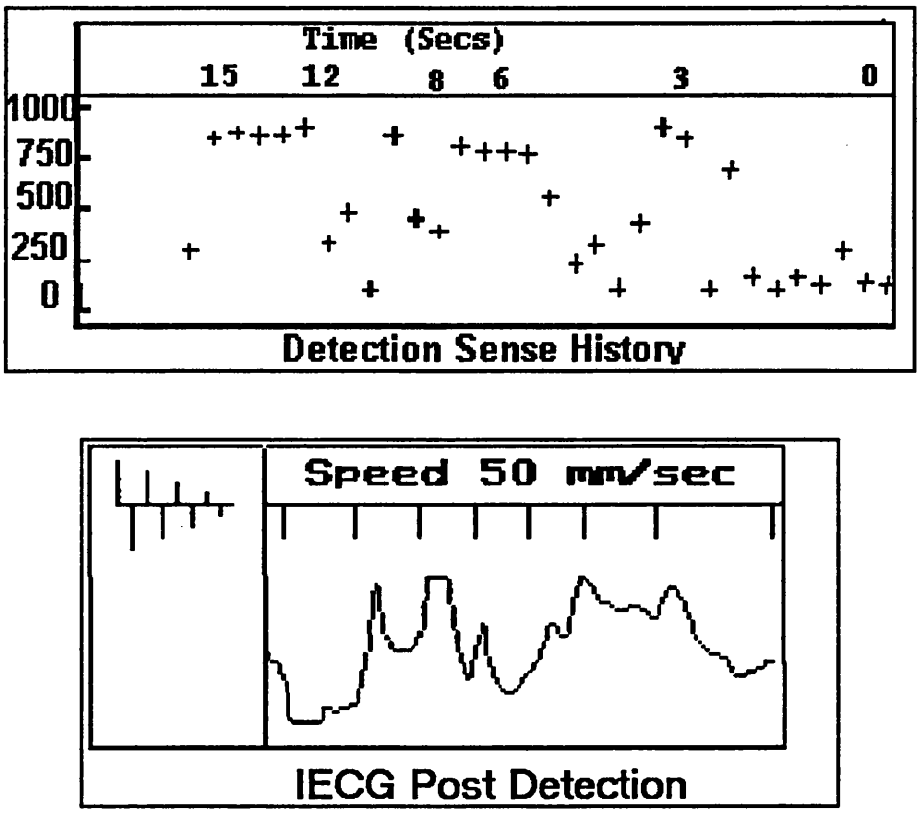

Figure 2.11: VF detection triggering a shock therapy in a patient with a Guardian 4210 defibrillator. The wildly varying cycle lengths (top) and jagged electrogram (bottom) suggested a broken sensing electrode. This was confirmed at system revision

A variety of ICD's have been used in patients in this study, reflecting the rapid development of new and improved devices. The main features of the ICD's used in this study are summarised in Table 2.1.

Table 2.1: ICD Generators used in this study

MANUFACTURER	CPI			MEDTRONIC	TELECTRONICS			VENTRITEX
MODEL	Ventak P Model 1600	Ventak PRx Model 1700	Ventak P2 Model 1625	PCD 7216A / 7217B	Guardian			Cadence
					4202	4210	4204	
First Implant at St. George's	1986	Jun 1991	Apr 1992	July 1989	Oct 1988	Dec 1989	Feb 1992	Sep 1992
Number Implanted	2	8	2	23	2	8	1	1
Bradycardia support pacing	-	+	+	+	+	+	+	+
Multizone detection	-	+	+	+	-	+	-	+
Antitachycardia pacing	-	+	-	+	-	+	-	+
Low energy cardioversion	-	+	+	+	-	+	-	+
Biphasic Shocks	-	-	+	-	-	-	-	+
Therapy counters	+	+	+	+	+	+	+	+
Event cycle length stored	-	+	-	+	-	+	+	-
Multiple event cycle lengths	-	+	-	+	-	+	+	-
Stored electrograms	-	-	+	-	-	+	+	+
NIPS/Fib induction system	-	+	+	+	-	+	+	+
Maximum shock energy (joules)	30	34	34	34	30	34	34	40
Weight (gm)	235	220	230	281/197	270	272	272	240
Volume (ml)	145	130	140	209/113	176	159	159	145

Manufacturers addresses and details of trademarked names are given in Appendix D

ICD Electrode Systems:

Epicardial System:

Until early in 1989 no endocardial electrode system was available for use in the United Kingdom and so the first eight ICD recipients in this study received epicardial systems electively. Subsequently a further 6 patients have received epicardial systems because of failure to achieve adequate defibrillation threshold with endocardial systems. Epicardial systems from three manufacturers (Medtronic, Telectronics and CPI (Cardiac Pacemakers Inc.)) have been used but they are all similar in type. Pacing and sensing is performed using two epicardial pace-sense screw-in electrodes. Defibrillating shocks are delivered via flexible patch electrodes which are sewn to the surface of the myocardium. These patch electrodes are available in 2 or 3 sizes (depending on the manufacturer) with conductive surface areas ranging between 350 and 850 mm^2. Generally two of these patch electrodes are used with the addition of a third only if needed to reduce the energy requirements for defibrillation. A typical patch electrode is shown in Figure 2.12.

Endocardial system:

There is greater variation in the individual endocardial electrode systems from the different manufacturers and so each manufacturer's system will be described separately.

Telectronics:

Two Telectronics transvenous electrode system have been used in this study. Their overall design is very similar. The early DF lead system was found to be very prone to lead fracture at the lead bifurcation and was replaced subsequently by the EnGuard™ lead system. The

system consists of two transvenous electrodes. The right ventricular electrode has a screw mechanism for fixing the tip of the electrode. The distal pace-sense electrode is situated at the tip of the lead behind the screw. Eighteen millimetres back from this ring electrode is a braided titanium defibrillation electrode with an area of 600mm^2. This acts as a defibrillation electrode and also as the anode for the pace-sense circuit. An atrial 'J' electrode forms the second component of the system. This electrode has a tined tip with a pace-sense electrode (which is not used in the present generation of defibrillators) and a titanium braid electrode 85mm back from this tip. When the lead is positioned like a conventional atrial 'J' pacing lead this defibrillation electrode lies in the superior vena cava. The third component of this system is a subcutaneous patch electrode (identical to this manufacturer's epicardial patch electrode) which is placed in the left axilla.

Medtronic:

The Medtronic Transvene™ electrode system again consists of two transvenous electrodes. The right ventricular electrode has a screw-fixation tip which is also the active electrode. Five millimetres proximal to this lies the anode ring which is used for sensing. The right ventricular defibrillation coil lies a further 8 millimetres proximal to this. The second transvenous lead carries a single coil electrode which floats in the superior vena cava. This system is usually used with the addition of an axillary subcutaneous patch. This patch is a modified epicardial electrode with a larger margin to allow easier fixation and to provide some protection for the ICD circuitry if an external defibrillation paddle is placed over the patch (Figure 2.12).

CPI:

The CPI Endotak™ system was the earliest of the transvenous electrodes. Unlike the other systems it consists of a single transvenous lead which carries both transvenous defibrillation

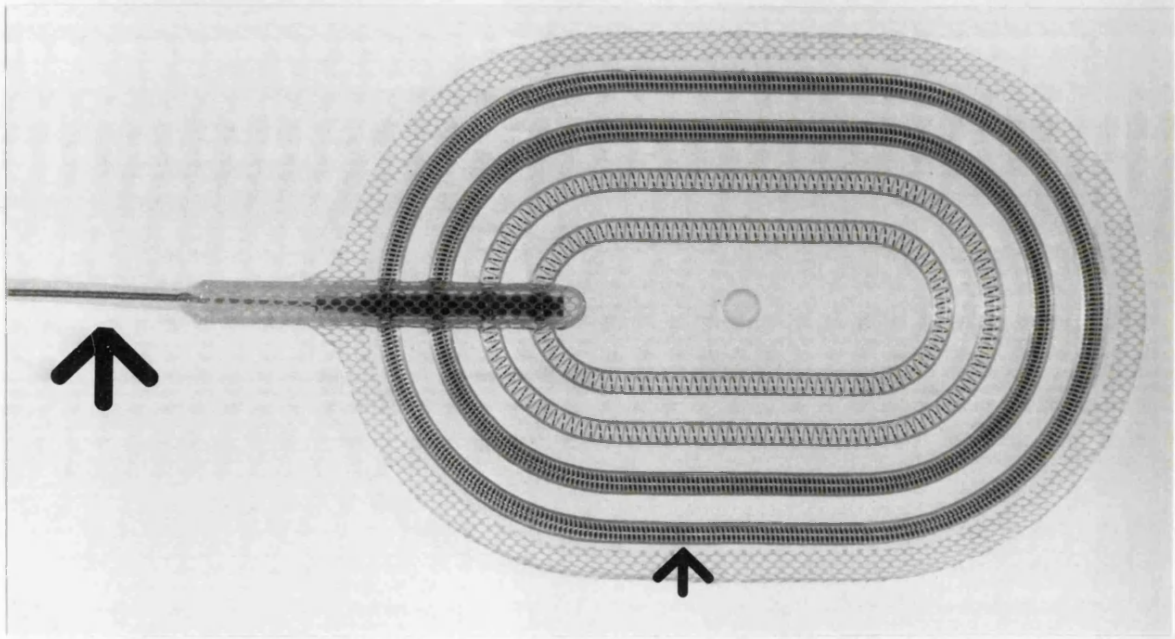

Figure 2.12: A typical epicardial patch electrode with multiple electrode coils (small arrow) and connecting lead (large arrow)

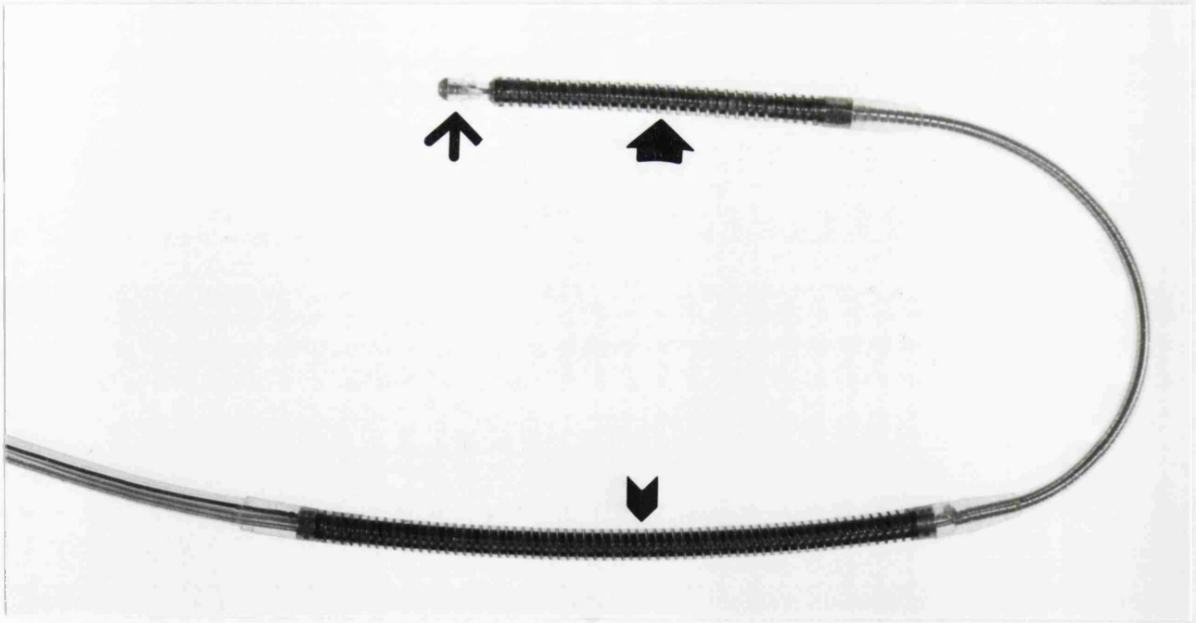

Figure 2.13: A CPI Endotak™ transvenous defibrillation electrode with a passive fixation pace-sense electrode at its tip (thin arrow), distal defibrillation electrode (thick arrow) and proximal defibrillation electrode (chevron)

electrodes. The initial series of trials showed a very high incidence of lead fracture (Hauser *et al.* 1992) and the lead was subsequently redesigned. It was this redesigned lead (the Endotak C) which was used in this study (Figure 2.13). This lead has a passive fixation tip with tines. A porous tip electrode is used for pacing and sensing and the right ventricular defibrillation coil lies 5 millimetres proximal to this. The proximal (superior vena cava) electrode lies a further 10cm proximal to the distal defibrillation electrode (The lead is available with different spacings of these two electrodes but all our patients received the 10cm spacing). This lead may be used alone, in conjunction with a conventional subcutaneous axillary patch electrode or, most recently, with a subcutaneous electrode array.

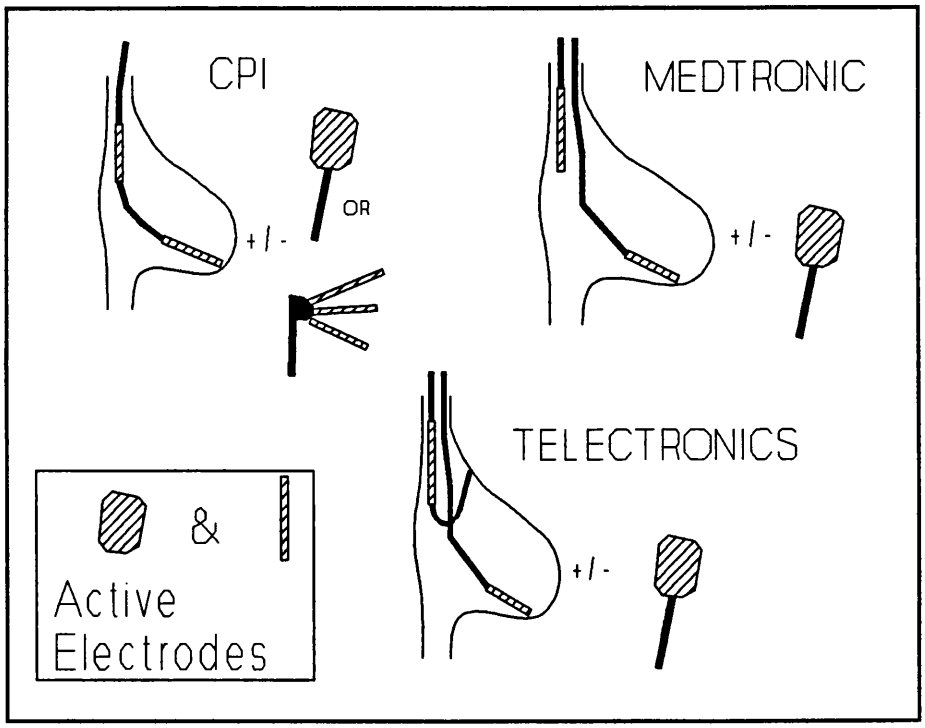

Figure 2.14: The electrode systems used in this study. Active electrode surfaces are shown striped. The CPI systems has a single transvenous lead and may use a subcutaneous axillary patch or array electrode. The other systems use two transvenous leads with or without a subcutaneous axillary patch

ICD electrode systems used for the patients' initial ICD implant are shown in Table 2.2

TABLE 2.2: LEAD SYSTEM		Telectronics	Medtronic	CPI
Epicardial	2-Patch	4	6	2
	3-Patch		2	
	TOTAL	4	8	2
Endocardial	Transvenous Leads Only			5
	Lead + Axillary Patch	7	15	
	Lead + Axillary Array			6
	TOTAL	7	15	11

Patient Inclusion Criteria:

All patients who received an ICD at St. George's Hospital between July 1986 and the end of September 1992 are included in this study. The precise indications for ICD implantation have yet to be defined and although the American Heart Association, European Society of Cardiology and North American Society for Pacing and Electrophysiology have recently defined guidelines for ICD use (See Chapter 1, Pages 28 & 29), during the bulk of the period of this study no clear published guidelines existed. In the early days of ICD implantation patients who received the device had to have survived two out-of hospital cardiac arrests to

justify taking the possible risks of ICD therapy. It is clear that to gain the maximum benefit from the use of the device and to outweigh any mortality or morbidity resulting from this use it should be implanted in patients at high risk of recurrent cardiac arrest in whom the risk of mortality from other causes is low. To some extent our definition of this group is limited by the lack of large population studies to define survival in various groups at risk. However there is a considerable volume of data available to enable a rational choice of some patients for treatment with an ICD.

Cardiac Arrest Survivors

A study of subsequent survival in 166 cardiac arrest survivors stratified by electrophysiological testing and left ventricular ejection fraction provides useful data (Wilber *et al.* 1988). These patients had no evidence of acute Q-wave myocardial infarction but 75% of the population had coronary artery disease. The survival curves for the different groups are shown in figure 2.15.

In this study low ejection fraction (≤30%) and the presence of an inducible arrhythmia at electrophysiological study were both associated with a higher recurrence rate of cardiac arrest. The suppression of inducible arrhythmias by antiarrhythmic drug therapy or the absence of an inducible arrhythmia appeared to be associated with better survival. Patients with an ejection fraction >30% and no inducible arrhythmia had a recurrent cardiac arrest rate of only 10% at 5 years suggesting that this group might be a low priority for ICD implantation. However a literature review of 54 patients with so-called idiopathic ventricular fibrillation suggested an 11% 1-year mortality for these patients (Viskin & Belhassen 1990) and implantation of the ICD in these patients was associated with a 28% incidence of appropriate shock therapy delivery in the first year (MIDAS investigators 1992). As this group is generally younger than the patients with coronary artery disease they may have more to lose and whether they should receive an ICD remains open to discussion.

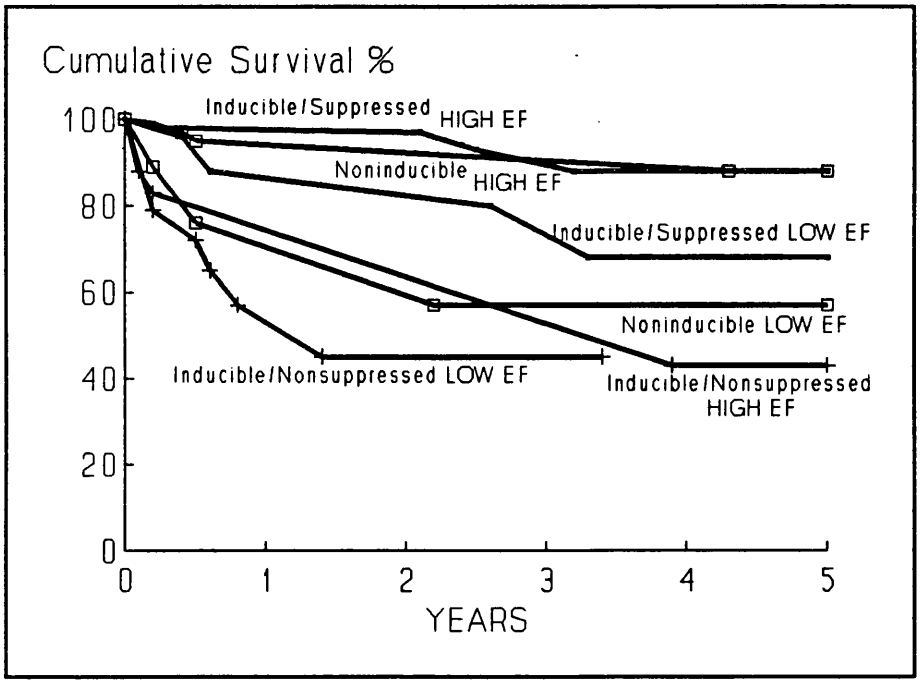

Figure 2.15: Survival after out-of-hospital cardiac arrest stratified by electrophysiological study and ejection fraction (From Wilber et al. 1988)

Congestive Cardiac Failure

In patients with congestive cardiac failure sudden unexpected death accounts for between 35 and 45% of all mortality (Packer M 1985). Many of the studies of congestive cardiac failure have failed to distinguish between patients with a primary cardiomyopathy and those with congestive failure due to coronary artery disease, making analysis of risk factors difficult. Approximately 65% of patients with dilated cardiomyopathy have an inducible ventricular arrhythmia (Borgreffe *et al.* 1992). However only about 30% of these exhibited a favourable response to antiarrhythmic drug testing and some studies suggest a high recurrence rate of ventricular tachycardia or fibrillation even in those patients not inducible at baseline (Liem & Swerdlow 1988).

It is clear that patients with dilated cardiomyopathy who present with out-of-hospital ventricular fibrillation or sustained ventricular tachycardia have a high risk of recurrent, life-threatening tachyarrhythmias and sudden death (Poll *et al.* 1984, Constatantin *et al.* 1989). The group which fails to respond to antiarrhythmic drug therapy would appear to be candidates for ICD implantation.

Hypertrophic Cardiomyopathy

Patients with hypertrophic cardiomyopathy (HOCM) have a 2-4% annual incidence of sudden death in adults and 4-6% in children (McKenna *et al.* 1981). There is little evidence that conventional programmed stimulation is of help in risk-stratification although a new stimulation protocol and method of analysis currently under development may be of benefit (Saumarez *et al.* 1992). The simplest marker of high risk in patients with HOCM is the presence of nonsustained ventricular tachycardia on Holter monitoring (McKenna *et al.* 1981). This has a sensitivity of 69% and specificity of 80% but the positive predictive accuracy is only 20%. Retrospective analysis suggests that the use of amiodarone may be associated with a more favourable outcome in this group (McKenna *et al.* 1985) although this remains controversial (Fananapazir *et al.* 1991). Patients with HOCM who present with sustained ventricular arrhythmias or cardiac arrest and who do not have an inducible arrhythmia at electrophysiological study or whose inducible arrhythmia is not suppressed by antiarrhythmic drugs are candidates for ICD insertion (Borgreffe *et al.* 1992).

The indications for ICD implantation in the present series of patients were:

1. *Patients presenting with sustained potentially life-threatening ventricular arrhythmias where suppressive antiarrhythmic drug medication could not be identified at electrophysiological study or where such therapy had failed clinically*

2. *Patients presenting with sustained ventricular arrhythmias where drug therapy could not be evaluated due to noninducibility at electrophysiological study and who were thought to be at high risk of recurrence.*

Patients were excluded if their ventricular arrhythmias were due to a reversible (ischaemic, toxic, metabolic) cause or if another therapy (such as arrhythmia surgery or catheter ablation) might be curative.

Patient Features:

During the period July 1986 to September 1992 48 patients (43 male and 5 female) were referred for ICD implantation. Their mean age at date of ICD implant was 46.9 years. The distribution of ages is shown in Figure 2.16.

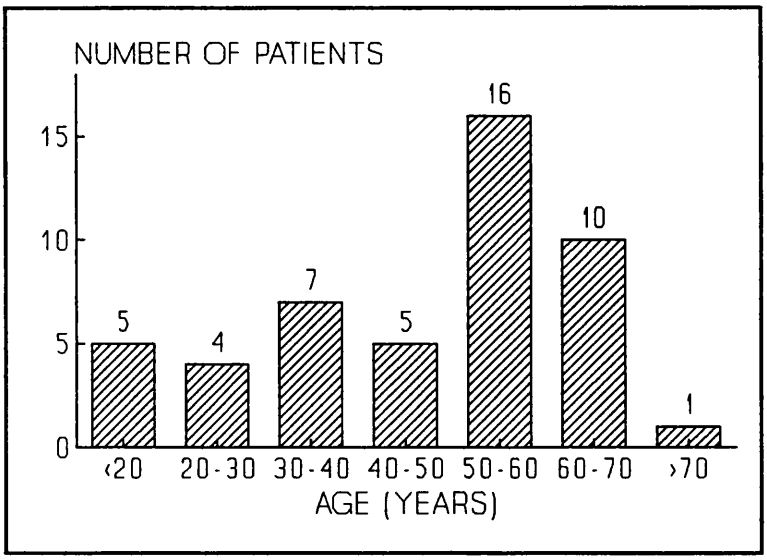

Figure 2.16: Age distribution of patients in whom ICD implantation was attempted

The three main patterns of presenting symptoms observed in these patients were, out-of-hospital cardiac arrest, sustained ventricular tachycardia and episodes of syncope due to self-terminating arrhythmias. Some patients exhibited more than one mode of presentation. Figure 2.17 shows the distribution of presenting symptoms.

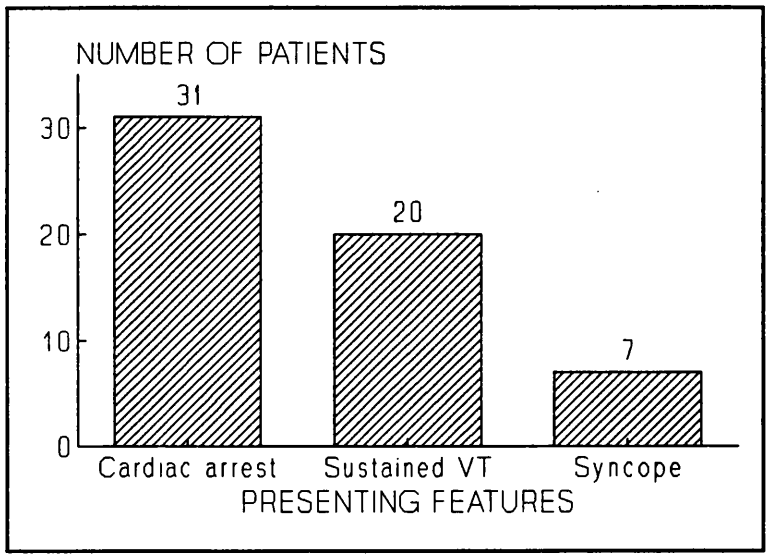

Figure 2.17: Distribution of presenting features amongst the 48 patients

There was a wide spectrum of underlying cardiac disease but overall the population had a different composition from that of most series of ICD recipients reported previously with a lower incidence of coronary artery disease and higher incidence of cardiomyopathy. The reason for this difference is unclear. Figure 2.18 shows the distribution of underlying cardiac disease in this population. The myopathy group was heterogenous with the diagnosis being made primarily on the basis of abnormal biopsies in eight patients and on the basis of impaired left, right or biventricular function in the other eight. The four "other" diagnoses were scleroderma (1), left main coronary artery arising from pulmonary artery (1), dystrophia myotonica (1), and mitral valve disease (1).

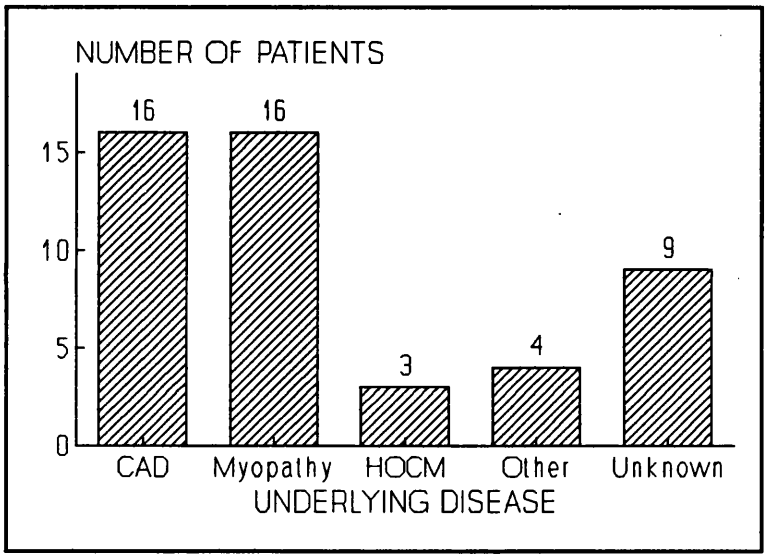

Figure 2.18: Distribution of underlying disease in the study population

There was a wide spread of left ventricular ejection fractions within these patients as shown in Figure 2.19.

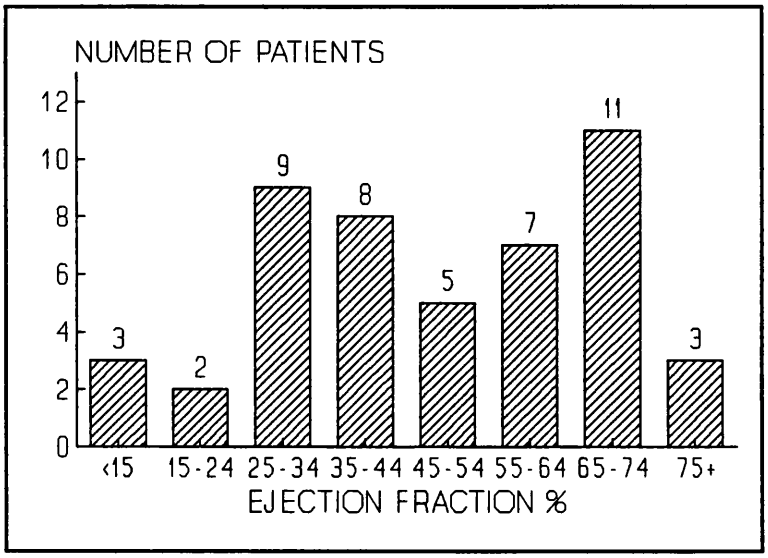

Figure 2.19: Distribution of left ventricular ejection fraction values within the population

Thirty of the 48 patients had an inducible ventricular arrhythmia at electrophysiological study (monomorphic ventricular tachycardia (22), polymorphic ventricular tachycardia (2), ventricular flutter/fibrillation (6)). The patients with monomorphic ventricular tachycardia had a mean of 4.05 trials of antiarrhythmic drugs against 0.76 drug trials per patient for the remaining patients.

Follow-up

The 47 patients who received an ICD have been followed for a mean period of 16.52 months. The distribution of follow-up is shown in Figure 2.20.

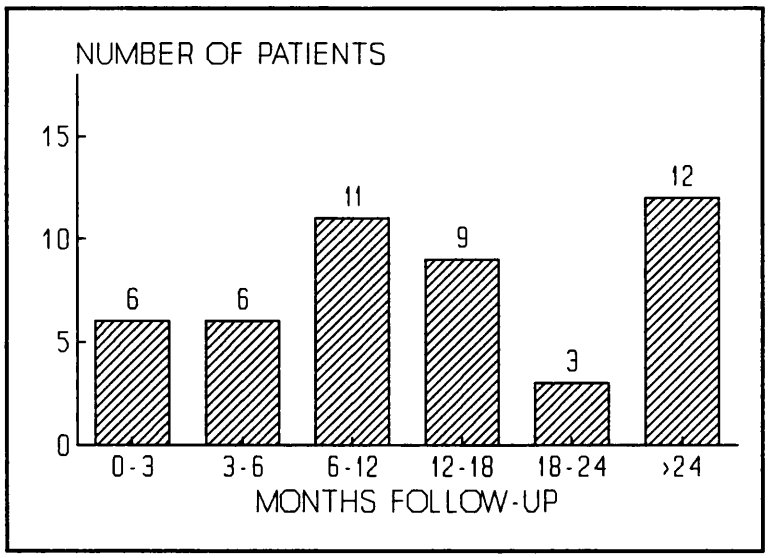

Figure 2.20: Distribution of follow-up of 47 ICD recipients

The 48 patients described above form the population for the analyses of ICD implant success, patient survival and therapy delivery which is the core of this thesis and whose outcome will be described in subsequent chapters.

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CHAPTER 3:

PATIENT-RELATED FACTORS PREDICTING THE SUCCESS OR FAILURE OF ATTEMPTED TRANSVENOUS DEFIBRILLATION LEAD SYSTEM IMPLANTATION:

Summary:

Twenty-seven of thirty-nine patients (69%) met a strictly defined criterion for defibrillation efficacy using a transvenous electrode system at ICD implantation. Univariate and stepwise analysis showed the heart diameter measured from the chest radiograph to be the most powerful predictor of a satisfactory defibrillation energy safety margin. The potential use of this variable as a means to identify in whom transvenous lead system implantation should not be attempted is considered.

Introduction:

Although the earliest human implantable defibrillation systems made use of an electrode in the superior vena cava (Mirowski *et al.* 1980) the demonstration of lower defibrillation thresholds with purely epicardial patch electrodes (Troup *et al.* 1985) lead to the initial predominance of this approach. However, the obvious drawbacks of the need for a thoracotomy and the considerable morbidity and mortality associated with this approach (Nisam *et al.* 1991b) ensured continued interest in transvenous systems. The excellent performance of early ICD systems in preventing sudden death (Echt *et al.* 1985) was already clear when the first trials of the Endotak™ transvenous electrode system began in 1986. It was important that a switch to transvenous electrode systems should be achieved without compromising the efficacy of the ICD. To ensure that efficacy was maintained a strict

criterion was defined, based on the defibrillation threshold at the time of lead implantation. Before considering the factors which may influence whether this criterion is satisfied in individual patients it is important to consider the concept of the defibrillation threshold in more detail.

The Defibrillation Threshold and Its Role at ICD implantation:

The success of a defibrillation shock depends on many factors including its energy and waveform, and the size and position of the defibrillation electrodes. It is obviously important to demonstrate at the time of ICD implantation that it is capable of defibrillating the heart from ventricular fibrillation. However we also need to know with a high level of certainty that the device will continue to be effective in the future. We know the energy and waveform which the ICD is capable of delivering and the position and size of the defibrillation electrodes is fixed. However the assessment of the reliability of defibrillation is affected by its essentially stochastic nature. A defibrillation shock of any given energy has a statistical probability of achieving defibrillation. Thus the defibrillation threshold is not a sharp barrier between energy levels which achieve defibrillation and those which do not. Instead it assumes the morphology of a pharmacological dose-response curve. The precise mechanism of this probabilistic character is unknown but may be related to variations in a "critical mass" of myocardium requiring defibrillation (Zipes *et al.* 1975), to conductive properties of myocardial cells (Jones *et al.* 1978) or systematic alteration of cellular or tissue electrophysiological characteristics involved in the initiation or perpetuation of ventricular fibrillation (Mower *et al.* 1974). At shock energies above the top of the curve defibrillation is always achieved whilst below the bottom of the curve defibrillation is never achieved. For shock energies which lie on the slope of the curve there is a certain probability of success at

any particular energy level. The defibrillation threshold may be defined as the E_{50} (the energy which will achieve defibrillation on 50% of occasions) or the E_{100} (the energy which will achieve defibrillation on 100% of occasions). To be sure of the long term effectiveness of defibrillation we need to be sure that E_{100} lies below the maximum energy output of the ICD (E_{ICDMAX}). Accurate definition of the dose-response curve for defibrillation requires multiple defibrillation attempts at various energies with the delivery of between 30 and 40 defibrillation shocks (Rattes *et al.* 1987), a procedure which is clearly impractical at human ICD implantation. Using sampling methods it is possible to define a point on the curve with a certain degree of statistical certainty. The difference between this energy level and E_{ICDMAX} represents the Apparent Safety Margin. However the Actual Safety Margin depends on the width of the defibrillation curve. Our knowledge of defibrillation curve widths stems largely from animal studies. In the dog the mean width of the curve between 20% success (E_{20}) and 80% success (E_{80}) is (0.85 ± 0.27) times E_{20} (Davy *et al.* 1987). Extrapolation of this width to that of the whole curve suggests a width between E_0 and E_{100} of (1.0 ± 0.3) times E50 (Singer *et al.* 1992a).

When designing our ICD implantation protocol our desire was to keep the number of ventricular fibrillation inductions to a minimum because of concerns about the potential effects of repeated ventricular fibrillation inductions on myocardial and cerebral function (Vlay 1987). Subsequently evidence of the potentially harmful cerebral effects of repeated VF induction has been published (Singer *et al.* 1992b) and myocardial function has been shown to be temporarily impaired after shock delivery (Broadhurst *et al.* 1993) although there is no evidence of myocardial necrosis (Elefteriades *et al.* 1992). When implanting the ICD we do not need to know the exact defibrillation threshold but only that there is an adequate Actual Safety Margin. Statistically one of the easiest ways to identify a point on the defibrillation curve with known confidence limits is to deliver three shocks at the same energy level (E_{3S}). Three successful shocks at any given energy defines with 95% confidence limits

a point on the defibrillation curve at or above the E_{40} (as 0.4 x 0.4 x 0.4 = 0.056) (Figure 3.1). It can then be calculated that to be 95% certain of being capable of achieving defibrillation on 100% of occasions we need to add 0.6 times the width of the defibrillation curve (= 0.6 x E_{50} or 0.6 x E_{40}/0.9 = 0.67 x E_{40}). Thus we need a shock of 1.67 x E_{40} to achieve this target. An additional safety margin is clearly desirable, both to allow for chronological variation in the defibrillation threshold and also for variation in the width of the defibrillation curve. A figure of 2.0 x E_{40} has been widely accepted as representing a satisfactory Apparent Safety Margin (Figure 3.1). This was our target figure in designing our

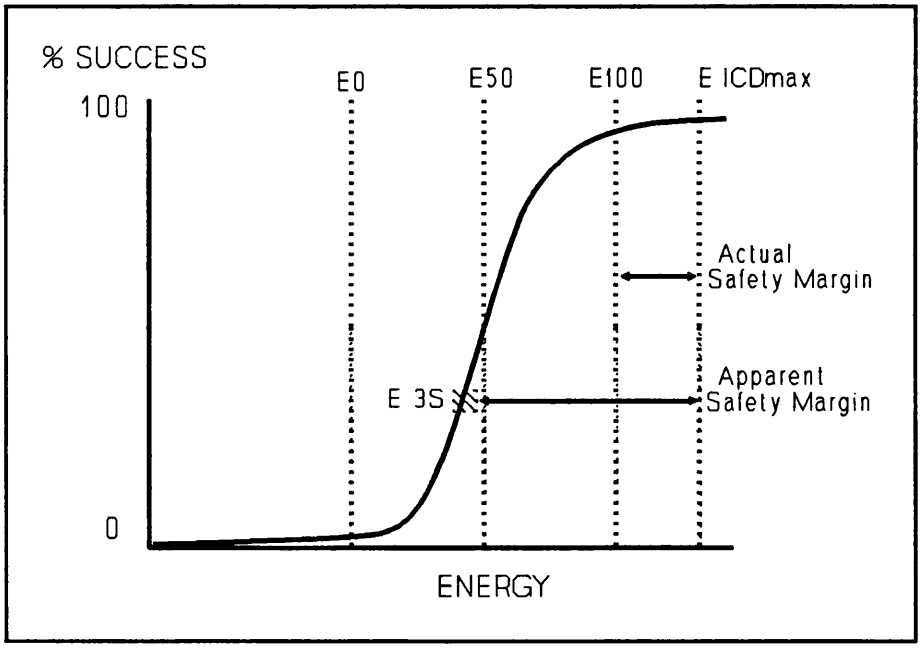

Figure 3.1: The defibrillation success / energy relationship. To ensure reliable defibrillation it is important that E_{ICDMAX} is greater than E_{100}. If three shocks at the same energy level achieve successful defibrillation this energy level defines a point E_{3S}, which has a 95% chance of lying above the E_{40} energy level. The apparent safety margin for the ICD is E_{ICDMAX} - E_{3S}. However the actual safety margin is smaller than this as E_{100} may lie up to 0.67 x E_{3S} above the energy of E_{3S} (see text for detailed explanation)

implantation protocol although some minor modification of this figure was enforced by some manufacturers implantation protocols and also by the varying maximum energy outputs of the defibrillators used in this study.

Factors which may determine the Success or Failure at ICD implant:

The primary aim of this study was to examine the patient-related factors which may determine the success or failure of transvenous ICD implantation. Because this study is based on the use of a number of different transvenous electrode systems it is important to consider the aspects of the ICD system which may influence outcome, in addition to the patient-related factors.

ICD related factors:

Three factors related to the ICD system may be of importance in the determination of the defibrillation threshold in these patients. These are:

1. Shock energy
2. Shock waveform
3. Electrode geometry (position, orientation, area)

In order to examine the impact of patient-related factors on success of transvenous defibrillation we would ideally like to keep these three factors constant. However, due to the investigational nature of the ICD systems used the choice of shock energy used to define the

defibrillation threshold was not ours. Medtronic specified an energy of 18 joules whilst CPI, Telectronics and Ventritex all used a threshold of 20 joules. Although we could have repeated the defibrillation testing at a constant energy for all devices our concerns about the risks of repeated defibrillation testing and the impact of previous defibrillation attempts on success at subsequent testing precluded this. We accepted that some degradation of our final analysis might result from this small difference. In view of the inherent variability of defibrillation thresholds based on three successful defibrillations at a given energy level the amount of additional variation introduced by this 2 joule discrepancy in shock output is likely to be small. Fortunately the same monophasic truncated capacitor discharge shock morphology was available for testing with all devices.

Electrode geometry is important in determining the distribution of current and voltage density generated by shock delivery through the electrode system. It is affected by the design of the electrodes and by their position within the body. Computerised tomographic scanning has shown that there is a relationship between the left ventricular mass encompassed by epicardial electrodes and the defibrillation threshold (Oeff *et al.* 1992). All defibrillation testing for this study has been performed with a standard electrode configuration using a cathode in the right ventricular cavity, an anode at the superior vena cava/right atrial junction and the addition of a second anode in the axilla if necessary. Despite using this standard configuration differences in body habitus will affect the precise geometry of the electrodes.

Patient specific factors which may affect the Defibrillation Threshold:

The prime aim of this study was to identify features which may predict the success or failure of a transvenous defibrillation system to reach a satisfactory safety margin in individual patients. The factors which we have considered include:

- Age
- Body habitus (weight, height etc.)
- Clinical presentation (cardiac arrest, sustained VT etc)
- Underlying cardiac disease
- Measures of heart size and function (i.e. ejection fraction)
- Inducibility of arrhythmia and response to antiarrhythmic drugs
- Antiarrhythmic drug use at the time of ICD implant

To minimise the impact of variations in electrolytes serum potassium in all patients was standardised to between 4.0 and 5.0 mmol/l and serum magnesium levels were in the normal range for all patients at the time of ICD implant. At the time that this study commenced no published data existed concerning transvenous defibrillation systems. However a certain amount of information was available from animal studies and epicardial defibrillation systems in man on factors affecting the defibrillation threshold, particularly concerning the possible effect of antiarrhythmic drugs.

Amiodarone - In the dog model the energy required for successful defibrillation has been shown to be reduced by acute intravenous amiodarone, whilst chronic oral administration had no effect (Fain *et al.* 1987). Chronic oral administration prior to ICD implantation has been variably reported to have no effect on defibrillation threshold at ICD implantation in man (Huang *et al.* 1991) or to be associated with higher defibrillation thresholds (Troup *et al.* 1985). Chronic oral adminstration of amiodarone following ICD implantation has been associated with a rise in defibrillation threshold, not noted in a control group taking type I antiarrhythmic drugs (Jung *et al.* 1992). Preliminary reports published since this study was commenced have not shown a significant higher defibrillation threshold in patients taking amiodarone at the time of transvenous ICD implantation (Ehrlich *et al.* 1992) although its impact on the chronic performance of transvenous defibrillation systems is as yet unreported.

Type 1A agents - In the limited studies which have been performed on these drugs neither quinidine (Dorian *et al.* 1986) nor procainamide (Deeb *et al.* 1983) have been shown to elevate defibrillation thresholds at clinically relevant doses.

Type 1B agents - Lignocaine has been shown to elevate defibrillation thresholds in dogs following acute intravenous administration (Kerber *et al.* 1986). The magnitude of this effect is related to the levels of the drug and to the anaesthetic agent used.

Type 1C agents - both Flecainide (Reiffel *et al.* 1985) and Encainide (Fain *et al.* 1986) have been shown to elevate defibrillation thresholds in animal studies.

ß-blockers - studies in dogs have shown a significant increase in defibrillation threshold following adminstration of propranolol, an effect that is reversed by isoprenaline (Ruffy *et al.* 1986). The effect of Propranolol may be related to its membrane stabilising action rather than to ß-blockade as timolol failed to cause a similar rise in defibrillation thresholds. Sotalol, with its combination of ß-blocking and type III activity has recently been reported to reduce defibrillation thresholds (Wang & Dorian 1989).

Underlying disease - In a study of sequential pulse defibrillation Jones and colleagues (Jones *et al.* 1987) found no difference in defibrillation thresholds between patients with coronary artery disease and those with Wolff-Parkinson-White syndrome (used as controls) at the time of cardiac surgery, despite a significantly lower ejection fraction in the cardiac disease group. Several other studies have failed to identify any relationship between left ventricular ejection fraction and defibrillation threshold using epicardial patch electrodes (Troup *et al.* 1985, Oeff *et al.* 1992).

A number of abstracts have been published recently in which analyses have been made of the factors predicting defibrillation thresholds achieved with transvenous defibrillation systems. These are summarised in the table 3.1.

Table 3.1: Published analyses of the factors predicting satisfactory defibrillation thresholds with transvenous defibrillation leads.

AUTHOR	n=	FACTORS PREDICTING SUCCESS	FACTORS WITH NO IMPACT ON SUCCESS/FAILURE
Ehrlich *et al.* (1992)	215	Female gender Higher LV ejection fraction Presenting arrhythmia VF	Amiodarone usage
Guarnieri *et al.* (1991)	53	Female gender Higher ejection fraction	Age Amiodarone use Coronary artery disease
Brooks *et al.* (1992)	59	Female gender Lower body weight Shorter height Smaller CTR	Ejection fraction LV end-diastolic diameter
Kopp *et al.* (1992)	68	No amiodarone use Absence of LV hypertrophy	Age Sex Presenting arrhythmia LV dimensions Chest dimensions
Brooks *et al.* (1993)	74	Smaller heart size on posteroanterior chest X-ray Female gender	Ejection Fraction Left ventricular dimensions

LV = Left ventricle VF = Ventricular fibrillation CTR = Cardiothoracic ratio

Patients and Methods:

Of the 48 patients included in this study 42 had attempted implantation of transvenous electrode systems. Three patients were excluded from this analysis of defibrillation efficacy because satisfactory pacing thresholds and R-wave amplitude could not be obtained and therefore they did not proceed to defibrillation testing. This left a total of 39 patients in this part of the study. Prior to consideration for ICD implantation all of these patients were extensively investigated to determine the nature of their underlying disease and to determine the most appropriate therapy for them. The individual values for each of the 25 variables recorded for each of the 39 patients considered in this study are listed in tabular form in Appendix A.

Age:

The Mean age of the 39 patients at the time of ICD implant was 47.5 years (range 15.9 to 74.7). The distribution of ages is shown in Figure 3.2

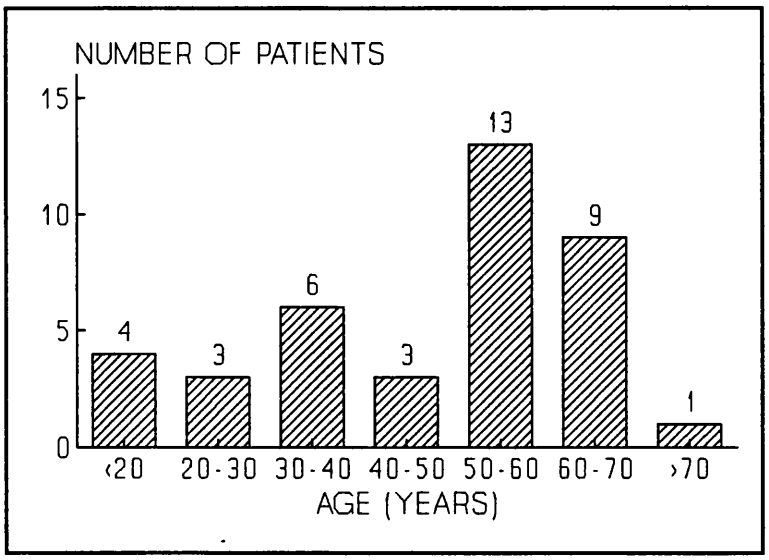

Figure 3.2: Distribution of ages in this population

Weight, Height and Body Surface Area:

The mean weight of the patients was 71.8 kg (range 50 to 102) and the mean height 169cm (range 158 to 154). Body surface area was calculated from the height and weight (Surface area ($Metres^2$) = $Weight(kg)^{0.425}$ x $Height(cm)^{0.725}$). Mean body surface area was 1.91m^2 (range 1.56 to 2.18m^2).

Presentation:

Three main patterns of presenting symptoms were noted:

1. Cardiac arrest - circulatory collapse due to very rapid ventricular tachycardia or fibrillation requiring resuscitation and defibrillation to restore circulatory function.
2. Sustained ventricular tachycardia with symptoms of palpitations, breathlessness, chest pain, dizziness etc.
3. Recurrent syncope associated with self terminating attacks of ventricular tachycardia.

A number of patients presented with more than one of these patterns (secondary presentation). The pattern of presentation of the 39 patients is summarised in Table 3.2.

Table 3.2: Mode of presentation of the 39 patients in this study

Primary presentation	n	Secondary presentation	n
Cardiac arrest	26	Sustained VT	6
		Syncope	4
Sustained VT	11	Cardiac arrest	0
		Syncope	0
Syncope/self-terminating VT	2	Cardiac arrest	0
		Sustained VT	0

Underlying disease:

All 39 patients underwent conventional coronary angiography, echocardiography and in the absence of significant coronary artery disease right ventricular biopsy. On the basis of the findings from these investigations the patients were classified into three diagnostic groups:

1. Coronary artery disease - significant coronary artery disease likely to account for any abnormality of myocardial function noted and likely to be the cause of the arrhythmia.
2. Dilated Cardiomyopathy - Evidence of significant right or left ventricular dilatation in the absence of significant coronary artery disease with or without abnormal right ventricular biopsy or normal ventricular function associated with an abnormal right ventricular biopsy.

3. Other - Hypertrophic cardiomyopathy, other cardiac or multisystem disease, or no identifiable cardiac disease.

Table 3.3: Distribution of underlying disease categories in the 39 patients in whom defibrillation with a transvenous lead system was assessed

Diagnostic Category	n
Coronary Artery Disease	13
Cardiomyopathy	14
Other	12
Unknown	(9)
Hypertrophic Cardiomyopathy	(2)
Mitral valve disease	(1)

Measures of Heart size and function:

The left ventricular ejection fraction was calculated from the right anterior oblique projection of the left ventricular angiogram using the Dodge single plane formula (Appendix C). The mean ejection fraction was 50.3% (range 8 - 83%). Left ventricular end diastolic dimension was taken from the short axis echocardiogram at the level of the mitral valve cusp tips. The mean value was 5.8cm (range 4.1 to 8.4cm). The heart diameter and cardiothoracic ratio were measured from the posteroanterior chest X-ray (Figure 3.3). The mean value was 0.52 (range 0.41 to 0.69).

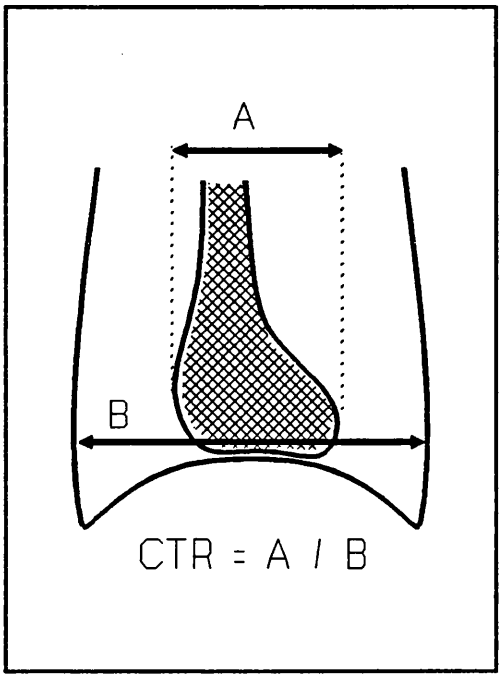

Figure 3.3: Method of measurement of heart diameter on the posteroanterior chest X-ray

Miscellaneous variables:

The mean pacing threshold of the right ventricular defibrillation electrode at implant was 0.58 Volts (range 0.2 - 1.2) at 0.5ms pulse duration. The mean endocardial R-wave was 12.0mV (range 2.0 - 24.5).

Eighteen of the 39 patients (46%) had inducible sustained ventricular tachycardia at stage 8 or lower of the Wellens protocol (appendix B) at electrophysiological study on at least one occasion during preimplantation investigation. The mean number of drug trials in these 18 patients was 3.89 (range 1 to 7).

Ten patients had a history of amiodarone usage within the week prior to implant and 17 patients had measurable levels of amiodarone in their blood (mean amiodarone level in these

patients was 1.03 mg/ml (range 0.1 to 2.3) and the level of its metabolite desethylamiodarone (DEA) was 0.94mg/ml (range 0.1 to 2.0)).

Implant Procedure:

All ICD implants were performed in a cardiothoracic operating theatre under general anaesthesia. No special pre-operative preparation was performed although we have recently adopted the use of betadine baths in an attempt to reduce the risk of infection. An arterial line was inserted in all patients and general anaesthesia induced with thiopentone and maintained with nitrous oxide and enflurane. Patients were paralysed with atracurium and ventilated. All patients received antibiotic prophylaxis with cefuroxime 1.5gm iv (or in case of Penicillin allergy or recent antibiotic therapy Vancomycin 500mg iv). The transvenous electrode or electrodes were placed via the left cephalic and or subclavian veins and X-ray screening used to confirm a satisfactory position within the heart (Figure 3.4). Pacing and sensing from the right ventricular lead was evaluated in accordance with the manufacturers recommendations. A threshold of less than 1 Volt at 0.5ms and an R-wave in excess of 6mV was regarded as acceptable (some manufacturers also required a slew rate in excess of 0.75 V/s). Interestingly in three of the patients in whom we were unable to implant a transvenous system this was because of inability to obtain satisfactory R-wave or pacing threshold despite multiple electrode positions being used. In 10 of the later patients in the series we evaluated defibrillation using the transvenous electrodes alone but normally we proceeded to implant an axillary patch electrode in a subcutaneous pocket prior to evaluation of defibrillation threshold. Ventricular fibrillation was induced either by connecting a standard cardiac fibrillator to the pace-sense electrodes of the right ventricular lead, or by increasingly rapid ramp pacing or if both of these techniques failed by delivering a low energy (25 joules)

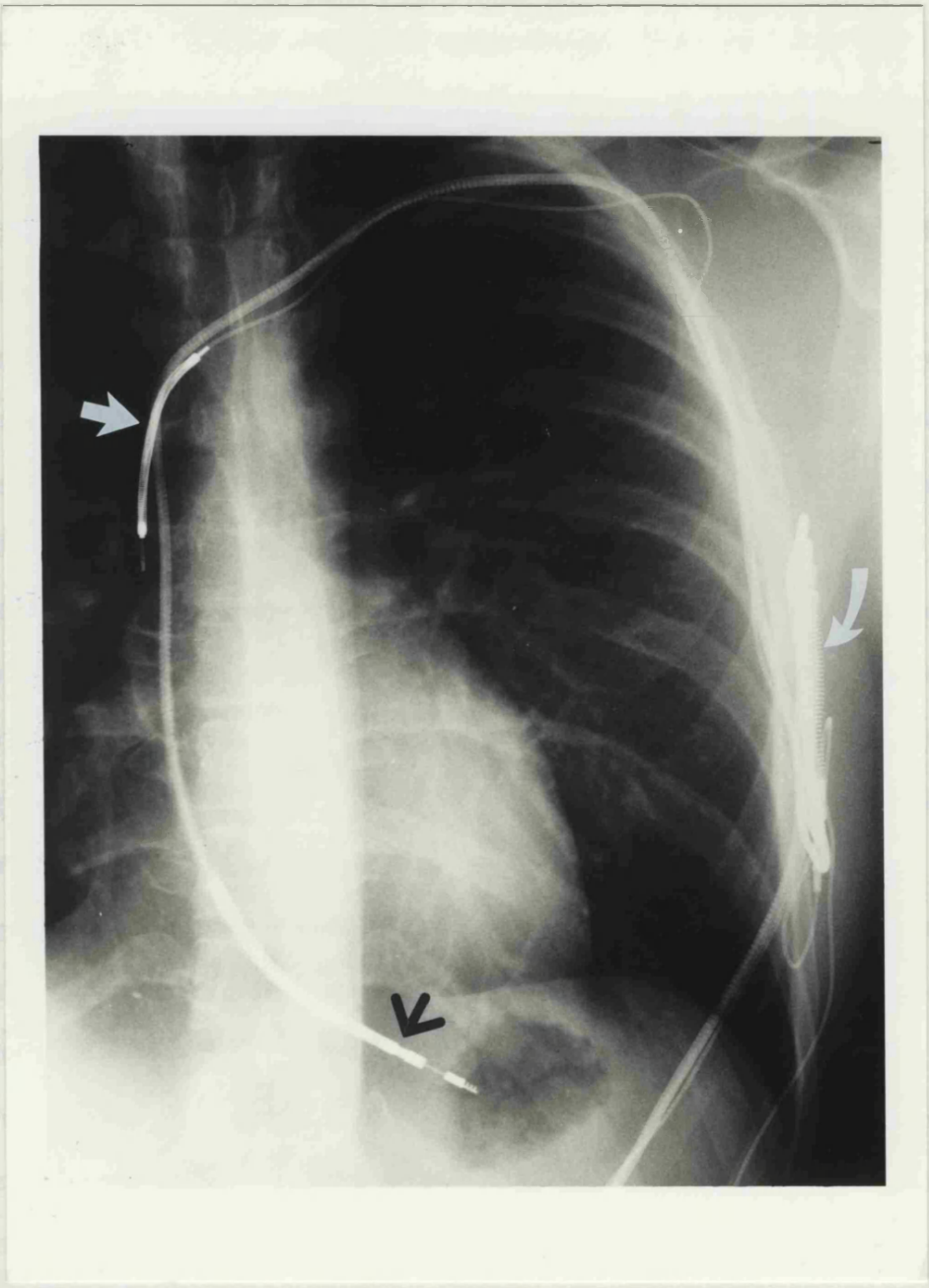

Figure 3.4: Radiological appearance of a transvenous electrode system. The right ventricular lead is positioned to lie well within the ventricle (black arrow) whilst the superior vena cava electrode tip is positioned at the junction of the superior vena cava and right atrium (white arrow). An axillary subcutaneous patch electrode can also be seen (curved white arrow).

external shock via the rescue defibrillation pads during rapid pacing (Appendix C). Once established ventricular fibrillation was allowed to continue for 10 seconds before delivery of the defibrillation shock via the defibrillation electrode shock system. Close control of the timing of the shock delivery was observed because of the well recognised effect of fibrillation duration on defibrillation threshold (Echt *et al.* 1988). If this shock failed to achieve defibrillation a second shock at maximum device output was delivered as soon as possible thereafter and if this shock also failed to defibrillate a rescue shock of 200 joules was delivered from the external defibrillator. When the initial defibrillation shock was successful a further two attempts at defibrillation at this energy level were made each separated by five minutes to allow full circulatory recovery. If these two attempts were successful then the defibrillation safety criterion was considered to have been met and the implant procedure continued. If one of these attempts failed then a fourth defibrillation attempt at the same energy was performed. If this was successful then the ICD was implanted but the defibrillation safety criterion was not considered met. If a second failure occurred at this energy level then not only had the defibrillation safety criterion not been met but further modification of the system was required. The defibrillation threshold testing protocol is summarised in Figure 3.5.

Provided the defibrillation safety margin was satisfied the transvenous leads were tunnelled subcutaneously (via the axillary patch pocket if one was used) to an abdominal pocket in which the ICD generator was placed. In all the patients who were evaluated for a transvenous electrode system this pocket was fashioned within the rectus sheath, either posterior or anterior to the rectus muscle. The transvenous leads were fixed at the venous insertion site using two electrode sleaves. Additionally the CPI Endotak™ lead was formed into a loop in a subcutaneous pocket adjacent to the venous entry site and both ends of the "strain relief loop" were fixed using electrode sleaves.

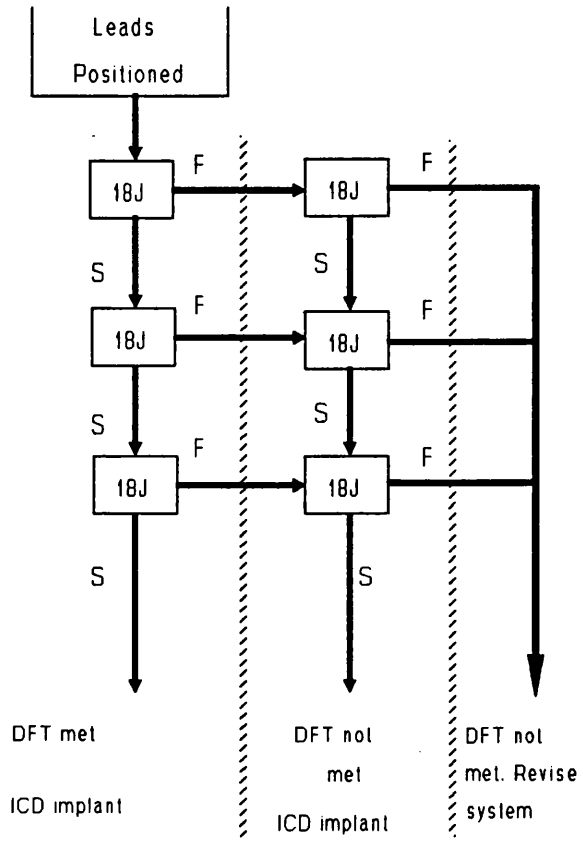

Figure 3.5: The defibrillation testing protocol [F=shock failure, S=shock success]. N.B. Shock energies of 20 joules were used with some devices - see text

A number of patients in this study had their transvenous defibrillation systems implanted despite failure to meet the defibrillation safety margin. Their outcome will be considered further in later chapters of this thesis. This present chapter concerns itself with the pre-operative features of the patient which are associated with achievement of this defibrillation safety margin.

Results:

Of the 39 patients who entered the protocol 27 (69%) met the strict defibrillation threshold criterion for transvenous system implantation (SUCCESS). The remaining 12 patients failed to meet the threshold criterion (FAIL). Seven of these 12 received a transvenous implant despite failure to meet the defibrillation threshold criterion because reliable defibrillation could be demonstrated with a safety margin of 10 joules below the maximum energy of the ICD which was being implanted. Four of the remaining five patients received an epicardial defibrillation system at a later date and one declined epicardial system implantation and has been maintained on antiarrhythmic drug therapy alone.

The individual patient variables have been analysed as univariate factors associated with success or failure in meeting the defibrillation criterion.

Age:

The distribution of patient ages between the SUCCESS and FAIL groups is shown in Figure 3.6. Mean age in the SUCCESS group was 42.96 years (sd = 16.9) and in the FAIL group 57.70 years (sd = 11.8). The difference between these two is significant (t=-2.73 p=0.0096).

Height, Weight & Body Surface Area:

Mean weight in the SUCCESS group was 71.6kg and in the FAIL group 72.2kg. Mean height in the SUCCESS group was 169.5cm and in the FAIL group 173cm. The difference between these was not significant and neither was the value of body surface area derived from them.

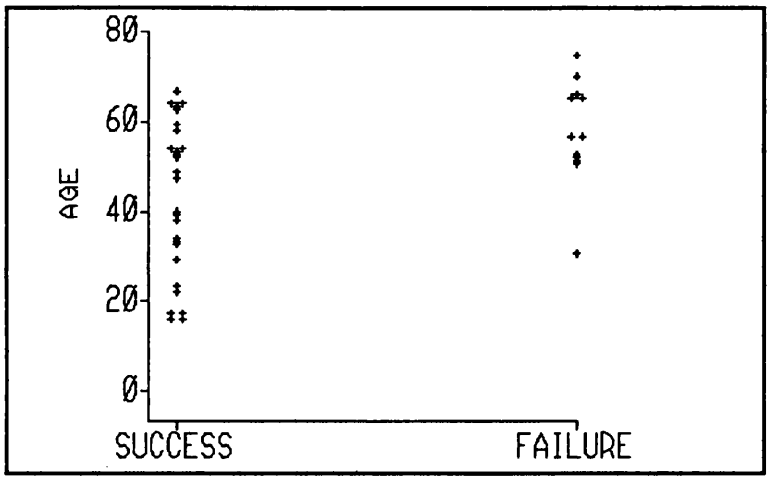

Figure 3.6 Scatter diagram of patient age in SUCCESS and FAIL groups

Presenting symptoms:

The distribution of presenting symptoms in the SUCCESS and FAIL groups are shown in table 3.4.

TABLE 3.4	Presentation		
Outcome	Cardiac Arrest	Sustained VT	Syncope
SUCCESS	19	9	7
FAIL	7	7	0
Chi-squared = 4.64 p=NS for whole table & between groups comparison			

Underlying Disease:

The distribution of underlying disease within the SUCCESS and FAIL groups is shown in Table 3.5.

TABLE 3.5	Underlying Disease		
Outcome	Coronary Disease	Cardiomyopathy	Other
SUCCESS	6	10	12
FAIL	7	4	1
Chi-squared for whole table = 8.94 p= nonsignificant Difference between Coronary Disease and Other groups is significant Chi-squared = 6.5 p = <0.05			

Ejection Fraction:

The mean ejection fraction in the SUCCESS group was 54.8% and in the FAIL group 40.3%. The distribution of ejection fraction in the two groups is shown in Figure 3.7. The difference is significant (t=2.14 p=0.0389).

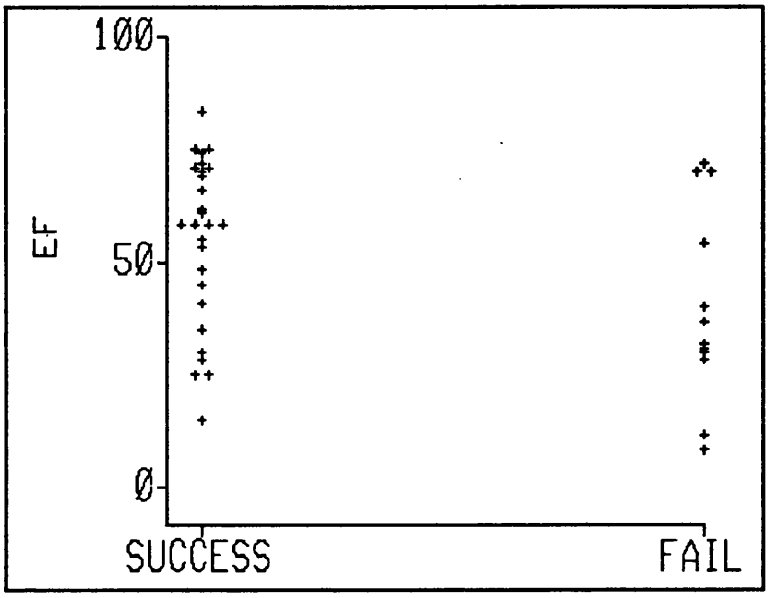

Figure 3.7: Distribution of the ejection fraction in the SUCCESS and FAIL groups

Left ventricular end diastolic dimension:

The mean left ventricular end diastolic dimension in the SUCCESS group was 5.53 and in the FAIL group was 6.36cm. This difference was significant (t=2.15 p=0.0383).

Cardiothoracic ratio:

The mean cardiothoracic ratio in the SUCCESS group was 0.504 and in the FAIL group 0.558. This difference is statistically significant (t=2.85, p=0.007). Mean heart diameter measured from the chest X-ray was 15.4cm in the SUCCESS group and 17.7cm in the FAIL group (p = 0.003). Mean chest diameter was 30.5cm in the SUCCESS group and 31.7 in the FAIL group (t = 1.33 p = NS).

Pacing threshold:

The mean pacing threshold in the SUCCESS group was 0.58V at 0.5ms and in the FAIL group it was 0.58V at 0.5ms. There was no significant difference between these figures.

R-wave amplitude:

The mean R-wave amplitude for the SUCCESS group was 11.3mV and for the FAIL group 13.7mV. This difference failed to reach statistical significance ($t=1.46$ $p=0.15$).

Inducibility of Ventricular Tachycardia at EPS:

Inducibility of ventricular tachycardia at electrophysiological study was significantly more common in the FAIL group than the SUCCESS group. The data is summarised in Table 3.6.

TABLE 3.6	Inducible	Noninducible
SUCCESS	9	18
FAIL	9	3
Chi-squared = 5.8 p = 0.016		

Amiodarone Usage:

There was no significant difference in amiodarone usage, amiodarone level (Amio. level), and DEA level in the SUCCESS and FAIL groups (Table 3.7).

TABLE 3.7	AMIODARONE USAGE	AMIO. LEVEL	DEA LEVEL
SUCCESS	6/27	0.37mg/ml	0.38
FAIL	4/12	0.71mg/ml	0.56
	Chi-squared = 0.11 p = NS	p = NS	p = NS

Type I Antiarrhythmic drug use:

There was no significant difference in Type I antiarrhythmic drug use between SUCCESS and FAIL groups (Table 3.8). However the very small number of patients taking these drugs at the time of ICD implant makes it impossible to rule out such an association.

TABLE 3.8	Type I Antiarrhythmic drug usage
SUCCESS	1/27
FAIL	3/12
Chi-squared = 2.11 p = 0.146	

Multivariate analysis:

The very limited size of our study population and the large number of variables severely limit the validity of using of multivariate analysis techniques with our data. Nonetheless, because many of the variables considered above are likely to be related to each other some form of multivariate analysis to indicate which of these variables contribute most to the final outcome is indicated. Because the outcome variable is qualitative and not continuous the most appropriate method is that of stepwise logistic regression analysis (Armitage & Berry 1987). Essentially each variable is considered in turn and a value found by repeated iteration which best succeeds in dichotomising the SUCCESS and FAIL groups. The variable which does so best is the one producing the largest Chi-squared statistic. The effect of adding the remaining variables to this primary variable is then examined with further iterations to see if they usefully improve the dichotomisation.

This analysis showed that the heart diameter in centimetres measured from the posteroanterior chest radiograph was the most powerful variable in predicting success or failure to achieve defibrillation thresholds at ICD implantation. The remaining 24 variables were discounted by the analysis as not contributing further to dichotomisation. If heart diameter was removed from the analysis then left ventricular end diastolic diameter became the most significant variable in dichotomisation. When this variable was removed as well left ventricular ejection fraction was the most significant dichotomising variable.

Discussion:

It has become clear since I started collecting the data for this study that transvenous defibrillation systems can offer many advantages over systems using epicardial patches. Foremost amongst these is a dramatic reduction in implant related mortality from the figures of around 3% (Nisam *et al.* 1991b) seen with epicardial systems to less than 1% with transvenous systems (Lindemans *et al.* 1991). The major drawback associated with transvenous defibrillation systems is the generally higher defibrillation thresholds associated with them. This manifests itself as the inability to achieve a satisfactory defibrillation safety margin in around 20% of patients in whom implantation is attempted (the proportion varies somewhat depending on how this safety margin is defined). In the early days of transvenous implantation such a failure was seen as an indication to proceed immediately to implantation of an epicardial patch system. This course of action was associated with a very high operative mortality of around 10% (Lindemans *et al.* 1991), to some extent cancelling out the benefits of the low mortality associated with the transvenous approach. By performing the epicardial implant at a later date some of this excess mortality can probably be avoided but the patient has still been exposed to an unnecessary transvenous implant attempt with its potential adverse medical and psychological impact. Accordingly it would be most useful if the success or failure of transvenous implantation could be predicted by a one or more preoperative variables. The univariate analysis described above shows a significant relationship between outcome and a number of preoperative clinical variables (age, presence of coronary artery disease, left ventricular ejection fraction, left ventricular end-diastolic diameter, cardiothoracic ratio, heart diameter on chest radiograph and inducibility of ventricular arrhythmia at electrophysiology study). Application of the logistic regression method identifies heart diameter measured directly from the posteroanterior chest radiograph as being the most powerful single variable in dichotomising the patients in whom transvenous

implantation will succeed from those in whom it would fall. The addition of information from the other variables did not contribute further to the separation. To consider whether this variable is sufficiently powerful to enable the identification of patients in whom the use of a transvenous defibrillation system should not be attempted we have performed receiver-operator analysis on our population. The sensitivity and specificity of a single value of heart diameter used as the dichotomising variable has been examined for all values of heart diameter noted in this population. The results of this analysis are shown in Table 3.9 and Figure 3.8.

Table 3.9: Sensitivity and specificity of heart diameter as a predictor of successful transvenous ICD implantation.

Heart diameter (cm)	Sensitivity	Specificity
12	1.0	0
14	1.0	0.222
15	0.833	0.444
16	0.833	0.519
17	0.75	0.704
18	0.417	0.778
19	0.25	0.963
20	0.25	1.0
22	0.083	1.0

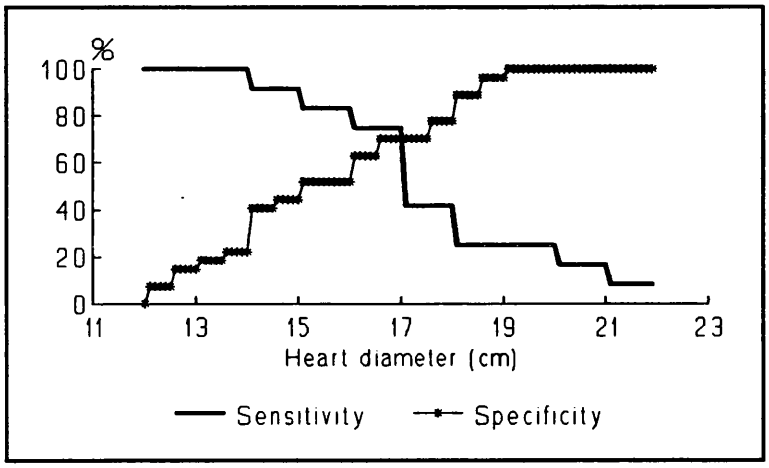

Figure 3.8: Receiver-operator curve for heart diameter used as a dichotomising variable between success and failure of transvenous ICD implants

Our prime aim in dichotomising this population is to avoid unnecessary attempts at transvenous ICD insertion inpatients in whom the likelihood of success is low. However it is also important not to deny the opportunity for a transvenous system to any patients in whom such a system would be successful as the adverse impact of this on overall mortality could easily cancel the gains produced by the avoidance of unnecessary transvenous implant attempts. This requires the procedure adopted to have a high specificity (approaching 1.0). As can be seen from the receiver-operator characteristic such levels of specificity are only approached at high values of the heart diameter (>19cm). Such values are associated with a sensitivity of 25% or less and thus the number of unnecessary transvenous implant attempts which could be avoided by the use of the heart diameter as a dichotomising variable is low. This finding is in accordance with other studies which have been published recently (see Table 3.1) which although they have identified variables associated with a higher risk of failure of transvenous defibrillation, none of these variables were of sufficient discriminant power to enable their prospective use. It is clear that the success or failure of transvenous defibrillation systems is influenced by many variables which we are currently unable to

measure (i.e. exact electrode geometry in relation to cardiac anatomy) and that no single or combined easily measured pre-operative variable is of use in identifying patients who should not receive a trial of a transvenous defibrillation system. For the moment therefore, all patients who require an ICD system should have an initial implant attempt using a transvenous system. The variables which I have identified above may nonetheless prove useful in providing patients with an indication of the likelihood of failure.

It is interesting to speculate why heart diameter measured from the posteroanterior chest radiograph has emerged as the most significant variable in this study and in another recently published study (Brooks *et al.* 1993). It may be that it provides a simple measure of heart "bulk". With a large and bulky heart it is more likely that some areas of myocardium may be exposed to lower field intensities, especially when endocardial electrodes are used.

A number of technical and medical developments have occurred during the course of this study which may reduce the need to identify patients who do not meet the conventional safety criteria for implantation of a transvenous ICD system.

Because of the potential safety advantages of transvenous defibrillation a number of centres (including ours) have relaxed their criteria for the DFT safety margin to accept three successes at 10 joules below the maximum output of the defibrillator. Whether such relaxation is associated with a higher risk of failure of defibrillation during spontaneous arrhythmia in the long-term remains to be seen but initial reports have not suggested that this is the case (Siebels *et al.* 1992). It is clear that when the DFT safety margin is further reduced to 5 joules or less there is an increased incidence of arrhythmic death during follow-up (Epstein *et al.* 1992). With the small size of our population there are insufficient patients in this group to be able to analyse whether the same variables influence this less critical definition of safety margin but it would seem likely that this is the case.

The second and more important development is the increasing availability of biphasic shock delivery from ICD's. The observation that biphasic shocks are superior to monophasic

shocks at achieving defibrillation dates back over twenty years (Schuder *et al.* 1964). Other reports of improved efficacy in animals followed (Fain *et al.* 1989). This difference has also been shown in man (Winkle *et al.* 1989b) and most recently with transvenous defibrillation electrode systems (Saksena *et al.* 1992). The difference is most marked at lower shock energies and may also be greater when ventricular fibrillation has been prolonged (Jones *et al.* 1989). Devices with biphasic shock are or will soon be available from all the major manufacturers of ICD's. Use of these devices has resulted in over 90% of patients reaching defibrillation safety margins in some centres (Block *et al.* 1993). This observation requires confirmation in multicentre studies but if realised would greatly reduce the number of failed transvenous implant attempts. It will be interesting to see whether the pattern of variables which are associated with success or failure remain the same or alters for this new shock morphology.

Limitations of this study:

The primary limitation of this study is the relatively small size of the population involved. This restricts the conclusions which may be drawn and particularly limits the analysis of the impact of qualitative variables (i.e. use of Type I antiarrhythmic drugs) which occur in a small proportion of the population. Nonetheless compared with larger populations the collection of the data by one person in a single institution may have advantages in terms of consistency of collection and classification of data. An additional limitation is imposed by the discrepancy in shock energies used to define the defibrillation threshold. Nonetheless the impact of this is likely to be small when compared to the variability due to the stochastic nature of the defibrillation threshold and variations in electrode geometry due to varying anatomy. Analysis of the proportion of successful implants with devices using the 18 joules criteria (13 of 20 attempts) versus devices using the 20 joules criteria (14 of 19 attempts) revealed no

significant difference (Chi-squared = 0.34, p=0.557). Finally it is important to stress that the conclusions drawn by the application of logistic stepwise regression to the data must be regarded as tentative in nature because of the large number of variables in relation to the number of subjects in the study.

Conclusions:

A strictly defined defibrillation safety margin criterion of three successive successful defibrillations at <20 joules is met by approximately 70% of patients at the time of implant of a transvenous defibrillation system using monophasic shocks. Univariate analysis illustrates a number of variables which are significantly associated with success or failure in meeting this threshold. Logistic regression analysis reveals heart diameter measured from the posteroanterior chest radiograph to be the most powerful variable in dichotomising the success and failure groups in our study although general extrapolation of this result is limited by our small study population. No other variable adds significantly to the dichotomisation provided by this one variable. Its superior performance compared to left ventricular ejection fraction or end diastolic diameter might be related to it providing an index of overall cardiac bulk rather than just simple left ventricular size. A larger more bulky heart may be more likely to have myocardium in areas of relatively low shock field intensity and in which fibrillation may not be successfully terminated. Unfortunately when used as a dichotomising variable it only achieves satisfactorily high specificity at low levels (0.25) of sensitivity. Therefore it will only identify a small proportion of patients in whom transvenous implantation will fail. The findings of this study are likely to be overtaken by the development of ICD's capable of delivery biphasic shock therapies which are associated with improved efficacy and by a relaxation of defibrillation safety criteria which even with monophasic shocks allows implant success rate of around 85%. Whether it will be possible

to identify in advance that small proportion of patients who will fail to achieve a satisfactory defibrillation threshold with transvenous leads despite the use of ICDs with biphasic shocks will have to await the results of studies involving many hundreds of ICD implants.

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CHAPTER 4:

A STUDY OF FACTORS ASSOCIATED WITH PATIENT SURVIVAL AND PATTERNS OF THERAPY DELIVERY:

Summary:

Forty-seven ICD recipients have been followed for an average of 17.02 months. Mortality and delivery of appropriate and inappropriate ICD therapies have been recorded and analysed to identify factors predictive of overall outcome. Poor cardiac function is an important factor related to mortality and delivery of appropriate therapies. The majority of inappropriate therapies are due to atrial fibrillation usually in the absence of a previous history of this arrhythmia. No factor predictive of this problem was identified.

Introduction:

The limitations of currently published survival studies in ICD recipients have been discussed in Chapter 1. The major issue remains does the ICD improve survival and if so by how much? Those studies which have been conducted have been performed in the United States in populations where coronary artery disease is the primary aetiology in >75% of patients. By contrast our population has a prevalence of coronary artery disease of only 33%. Additionally these published studies have been based almost entirely on the use of first generation ICDs with no data logging facilities. This renders the identification of the arrhythmia precipitating therapy delivery extremely difficult. In this study over 90% of patients received third-generation ICDs capable of at least some form of data logging. This provides a greater opportunity for the correct classification of arrhythmic episodes although

the data stored does not always enable the reconstruction of an unequivocal sequence of events leading up to therapy delivery.

The actuarial incidence of therapy delivery by ICDs remains an area of considerable interest. If we are satisfactorily able to identify a high risk group of patients to receive the ICD then a large proportion of patients should receive therapies from their device in the early post-implantation period. The pattern of therapy is also a critical factor in determining the quality of life for patients with an ICD. Fogoros *et al.*(1989) reported a first year cumulative shock therapy incidence of 51% rising at 4 years to 81%, but their study was conducted using first generation devices and the separation of spurious from appropriate shock therapies was limited. Appropriate shock therapies were received by 33% ofl patients at one year rising to 64% by four years. In Levine's (Levine *et al.* 1991) study 53% of patients had received an appropriate therapy delivery after a mean follow-up of 9.1 months. No long-term follow-up has been published for third generation devices although a 58% therapy delivery rate has been reported at a mean follow-up of 9 months (Fromer *et al.* 1992).

There has also been considerable interest in factors which predict subsequent mortality and therapy delivery in patients receiving an ICD. Most studies agree that impaired left ventricular function is associated with impaired total survival although the ICD appears equally effective at preventing sudden arrhythmic death in patients with poor left ventricular function (Edel *et al.* 1992, Kim *et al.* 1992). Some studies (Zilo *et al.* 1991) have suggested that the occurrence of an ICD shock is itself a risk factor whilst other have not (Gross *et al.* 1991b) but neither of these studies are corrected for the possible confounding effect of differing left ventricular function in the two groups. Presentation with sustained ventricular tachycardia has also been reported as a poor prognostic sign (Edel *et al.* 1992) whilst coronary artery bypass grafting has been associated with improved long-term survival (Levine

et al. 1991). Whilst most studies have reported very low sudden death rates in ICD recipients one study which reported a 5-year cumulative sudden cardiac death rate of over 30% at 4 years suggested that a presentation with sudden cardiac death was itself a powerful risk factor for subsequent sudden death (Gross *et al.* 1991a). Other studies have not replicated this finding.

Impaired left ventricular function has also been shown to be a predictor of a higher likelihood of receiving a shock therapy from the ICD and of a shorter elapsed time before shock therapy delivery (Levine *et al.* 1991, Reiter *et al.* 1991). ß-blocker therapy and coronary artery bypass grafting at the time of surgery have been associated with a lower subsequent incidence of shock therapy whereas the signal averaged ECG recorded prior to ICD implant has not been shown to be effective in predicting subsequent shock delivery (Epstein *et al.* 1991). The impact of antiarrhythmic drug therapy on the pattern of ICD therapy delivery has also been of interest. One study showed no difference in shock therapy delivery between patients receiving amiodarone and those who were not (Huang *et al.* 1991) whilst the CASCADE study showed a lower incidence of shocks in the amiodarone treated subjects amongst a group of 228 patients who were randomized to either amiodarone or "conventional" electrophysiologically guided antiarrhythmic drug therapy (Dolack *et al.* 1992).

One of the major areas of concern with the ICD remains the incidence of inappropriate therapy delivery, due either to atrial fibrillation, supraventricular arrhythmias, sinus tachycardia on exercise or to problems with the sensing electrode system. Inappropriate therapies can be a significant factor in stimulating the occurrence of further ventricular arrhythmias (Johnson & Marchlinski 1991). Fogoros *et al.*(1989) reported a spurious shock incidence of 17% at one year rising to 21% by four years but a large number of the shocks delivered in this study could not be definitively classified as appropriate or inappropriate because of the limitations of the first-generation devices used. Several other studies have reported inappropriate therapy delivery in approximately 20% of ICD recipients (Winkle *et*

al. 1989a, Maloney *et al.* 1991, Wietholt *et al.* 1993). Only the FDA submission for the Ventak P ICD has reported the surprisingly low rate of 3% (Nisam *et al.* 1991a) most probably due to under-reporting. This study provides the opportunity to examine the incidence of inappropriate therapies in a population with mainly third-generation ICDs and also to analyse the factors which may be associated with inappropriate therapy delivery.

Patients and Methods:

The analysis of survival and therapy delivery in this chapter is based on the 47 patients who received an ICD implant at St. George's Hospital between July 1986 and September 1992. Follow-up data for these patients is available until December 15th 1992 and the mean period of follow-up is 17.02 months (range 2.5 - 77.0 months). Thirty-three of the patients have transvenous electrode systems and fourteen have epicardial patch systems (a detailed description of the systems used is provided in Chapter 2). Because epicardial systems were initially used for all implants the mean period of follow-up with these systems is longer (mean 32.5 months) than for transvenous systems (mean 10.5 months). Total patient exposure to the two systems is quite similar with 454 patient-months of epicardial system and 345 patient-months of transvenous system experience.

Information on over 30 potentially important variables has been analysed in this study. These variables fall into three main groups. *Patient specific variables* such as age, left ventricular ejection fraction and ongoing antiarrhythmic drug therapy. *Implant related variables* such as procedure time, device manufacturer, whether transvenous defibrillation safety margin was met and subsequent procedure related complications such as system infection. *Management related variables* such as continuation of antiarrhythmic drug therapy, use of ß-blockers, device programming (i.e. single or multizone therapies) and the margin

between sinus tachycardia and ventricular tachycardia rates. The individual variables used in this analysis are summarised in Table 4.1.

Table 4.1: Variables used in the analysis of survival and therapy delivery

Patient related variables	Age Presentation (Cardiac arrest, sustained VT etc.) NYHA status Underlying Disease Previous - PTCA - CABG - VT surgery/ablation Inducible arrhythmia at EPS Number of antiarrhythmic drug trials Left ventricular ejection fraction Left ventricular end diastolic diameter Heart diameter on chest radiograph Late potentials on signal-average ECG
Implant related variables	Epicardial / transvenous system Procedure time Screening time Device manufacturer Early complications Late complications System revision / removal / replacement
Management related variables	Number of detection zones programmed Antitachycardia pacing / Cardioversion Continued antiarrhythmic drugs / ß-blocker

Methods:

Overall cumulative survival was calculated using the Kaplan-Meier method (Kaplan & Meier 1958). Where statistical comparison has been made between cumulative survival in different groups the Logrank test has been used (Mantel 1966). For statistical analysis of single variables three tests have been used. For variables where the assumption of a normal distribution is reasonable the unpaired t test has been used, for those where normality may not be assumed the Mann-Whitney U test has been used and for discontinuous variables the Chi-squared test has been used. Although the relatively small population studied restricts the application of multivariate techniques very limited use has been made of the Cox proportional hazards model (Cox 1972) to examine the relationship between variables. This technique will select the variable which accounts for the most variation in the dependent variable, calculate the relative risk of possession of this variable and then examine the remaining variables to see whether they contribute further to the overall prediction of the value of the dependent variable. It is able to handle both continuous and discontinuous variables.

Definitions:

The following definitions have been applied throughout this chapter -

Survival - survival free of death from any cause

Sudden cardiac death - death from a cardiac cause where the duration of the terminal event was less than one hour.

Sudden arrhythmic death - death from an arrhythmia where the duration of the arrhythmic event was less than one hour

Nonsudden cardiac death - death from a cardiac cause where the duration of the terminal event was more than one hour

Noncardiac death - death due to noncardiac disease

Appropriate therapy - an ICD therapy which following analysis of the stored electrograms, data logs and the patient's history appears to have been appropriately delivered for a ventricular arrhythmia.

Inappropriate therapy - an ICD therapy which following analysis of stored electrograms, data logs and the patients's history appears to have been delivered inappropriately, either as a result of a supraventricular arrhythmia or due to a malfunction of the ICD or its lead system.

Life-saving therapy - an appropriate therapy delivered by the ICD for an arrhythmia which on the basis of the electrograms, data logs and patient's symptoms and the history of previous similar episodes had a high likelihood of a fatal outcome (clearly such a definition is subjective but may be a more appropriate way of assessing survival in the absence of the ICD than the assumption used in other studies that the first

appropriate shock therapy delivered by the ICD is life-saving).

Results:

Total Survival:

Total survival of the 47 patients is shown in Figure 4.1

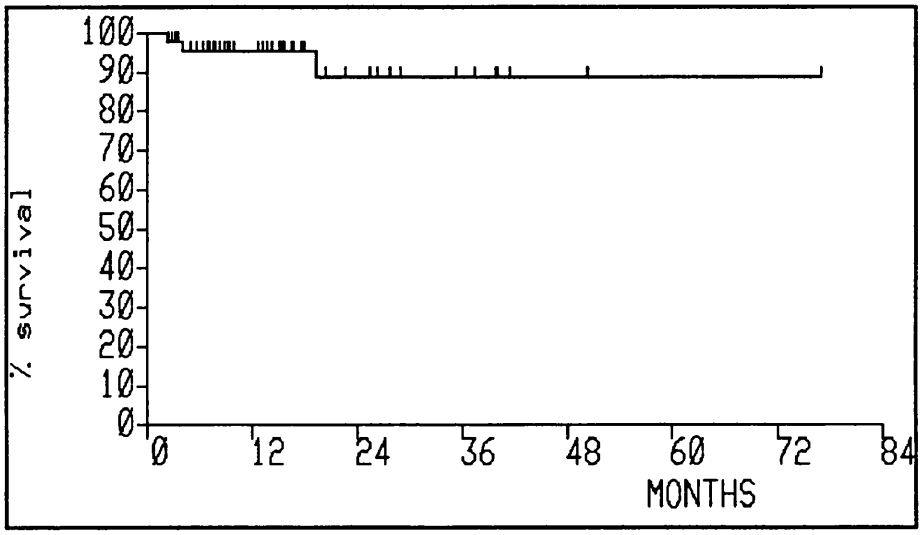

Figure 4.1: Total survival free of all causes of mortality in the 47 ICD recipients

Survival at 12 months is 95% falling to 88% at 24 months and remains at this level out to 72 months. Survival free of sudden arrhythmic death is 100% throughout this period as no patient in this population died by this means.

Comparison of expected and actual survival:

Analysis of arrhythmia episodes using the definition of life-saving therapy defined above suggests that 10 of our 48 patients have received life-saving therapies during the period of this study. Figure 4.2 shows the mortality from sudden cardiac death which would have been expected had these deaths occurred compared with that actually seen (0%). This difference is highly significant (Chi-squared = 10.6, p = 0.001) and suggests that the ICD has produced a substantial reduction in sudden cardiac death.

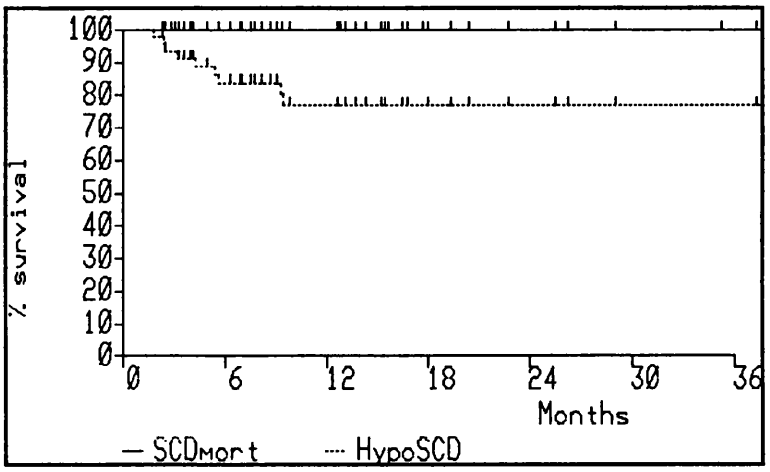

Figure 4.2: Expected (HypoSCD) versus actual (SCDmort) survival free of sudden cardiac death in 47 ICD recipients

Because nine of the ten patients who received life-saving therapies remain alive the impact of the device on total survival has been similar. Again survival with the ICD is better and the difference is significant (Chi-squared = 5.34, p=0.02).

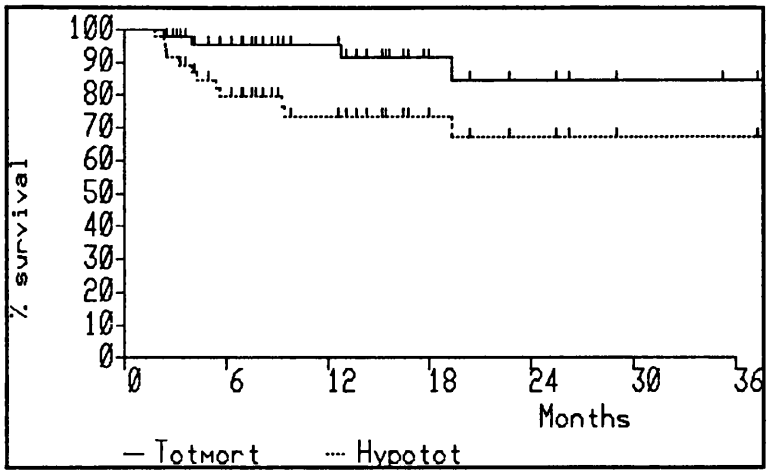

Figure 4.3: Expected (Hypotot) versus actual (Totmort) total survival in 47 ICD recipients

ANALYSIS OF THE FACTORS ASSOCIATED WITH OVERALL SURVIVAL:

Patient specific variables -

Age

The mean age in surviving patients was 45.4 years whilst in those who died it was 56.0 years. However patient age was widely distributed in our population and this difference was not significant ($p = 0.21$).

Left Ventricular Ejection Fraction

Mean ejection fraction in the survivors group 51.0 and in the nonsurvivors 28.0 ($p < 0.03$). If ejection fraction is treated as a dichotomised variable about a value of 30% the substantial difference between survival in the two groups is clearly seen.

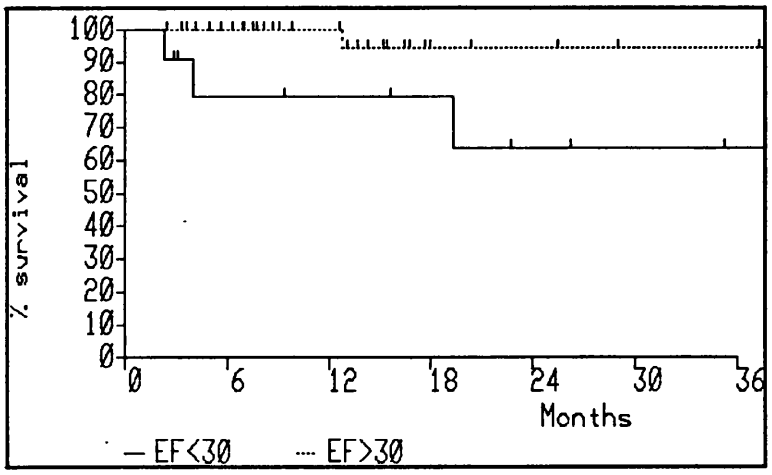

Figure 4.4: Survival stratified by ejection fraction >30% (EF>30) versus ≤30% (EF<30)

This difference in survival between the dichotomised groups is significant (p>0.03) by the Logrank test.

Heart Diameter on Chest X-ray:

Although mean heart diameter is smaller in survivors than non survivors (16.0 v.18.4 cm) the difference is not significant.

Underlying Heart Disease:

This was stratified into coronary disease, cardiomyopathy and no known cardiac disease categories as described in chapter 2. No individual category had a statistically significant difference in mortality. However when the "other" and cardiomyopathy groups were joined and compared with patients with coronary artery disease a difference was apparent.

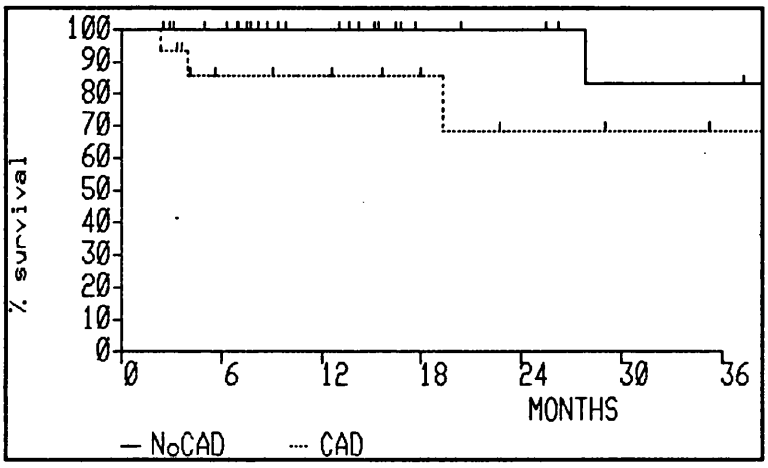

Figure 4.5: Survival in ICD recipients with coronary artery disease (CAD) or no coronary disease (no CAD)

Although mortality appears higher in the patients with coronary artery disease when compared with patients with cardiomyopathy or no known cardiac disease the logrank test fails to reach statistical significance (Chi-squared = 3.28 with 1 d.f. p = 0.07). The mean ejection fraction in the coronary artery disease group (39%) is significantly lower ($p<0.03$) than that in the no coronary artery disease group (53%) offering a possible explanation for much of the observed difference in survival.

Functional status:

All patients were graded by functional status into New York Heart Association (NYHA) grades 1 to 4 (Criteria Committee, New York Heart Association). Survival was significantly better ($p <0.005$) in the patients in NYHA grades 1 & 2 (n=43) than in the patients in NYHA grades 3 (n=4) and also significantly better in grade 1 than grade 2 (p=0.05). No patient was in NYHA grade 4 at the time of ICD insertion.

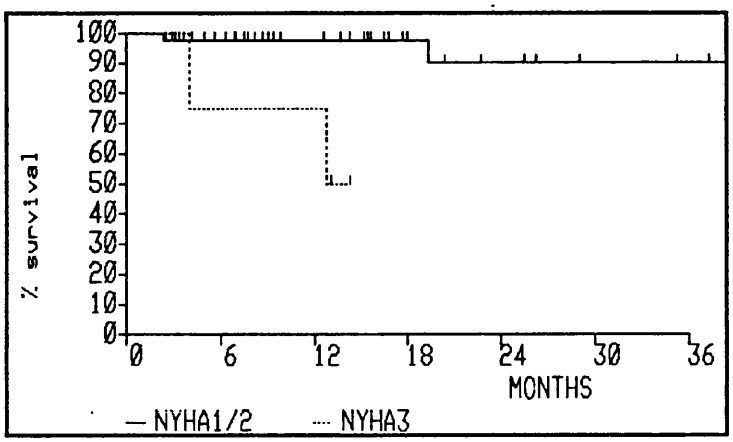

Figure 4.6: Survival stratified by NYHA status (Grade 1/2 or 3) at the time of ICD implant

Pattern of presentation:

There was no significant difference in total survival between patients presenting with cardiac arrest, sustained ventricular tachycardia or in other ways.

Inducible arrhythmia at electrophysiological study:

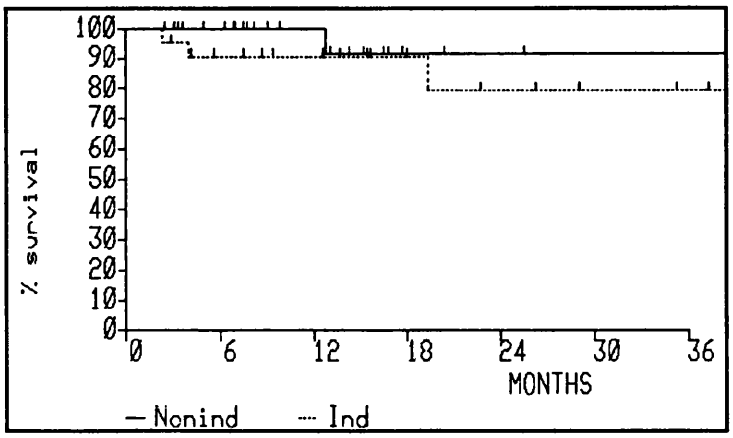

Figure 4.7: Survival stratified by inducibility of ventricular arrhythmia at electrophysiological study (Ind = Inducible, Nonind = Noninducible)

There was no significant difference in survival between patients with and without inducible arrhythmia at electrophysiological study (p=NS).

Implant Related Variables:

Epicardial and Transvenous defibrillation systems:

There is no significant difference in survival between patients with epicardial and transvenous lead systems (p=NS).

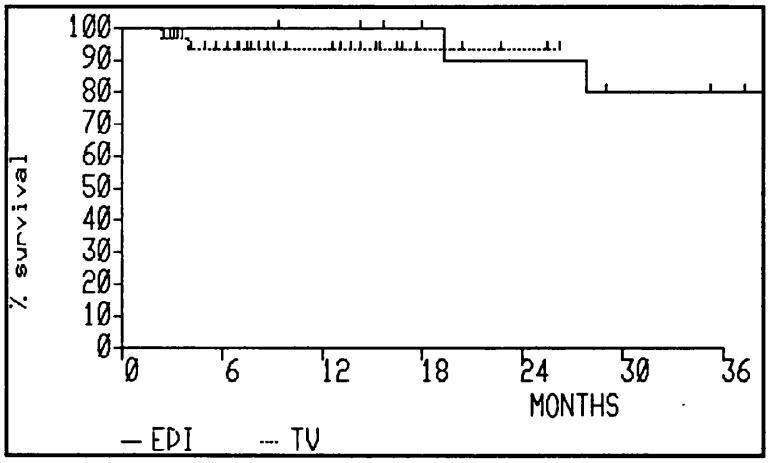

Figure 4.8: Survival with epicardial (EPI) versus transvenous (TV) ICD system

Failure to meet defibrillation safety margin (as defined in Chapter 3) at ICD implant also has no significant impact on survival (Figure 4.9).

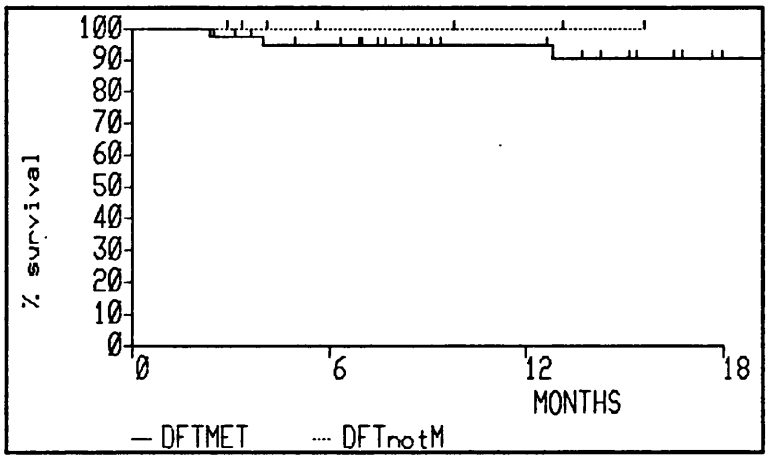

Figure 4.9: Survival stratified by whether the defibrillation safety margin was met (DFTMET) or not met (DFTnotM) at ICD system implant

Device Manufacturer:

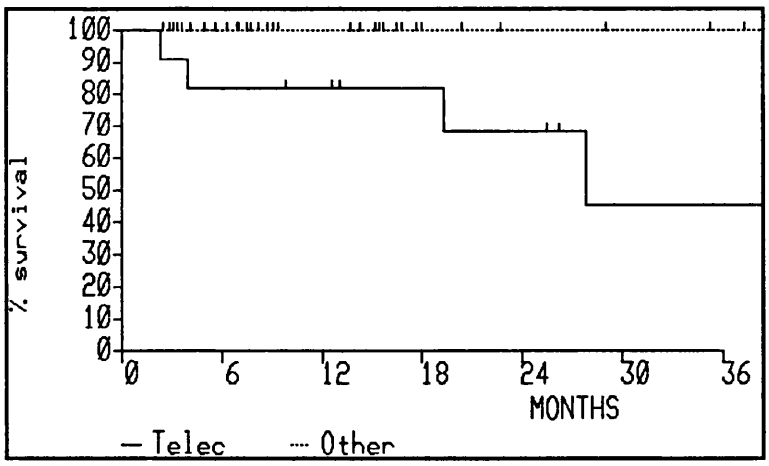

Figure 4.10: Mortality stratified by ICD manufacturer (Telec - Telectronics, CPI, Medtronic & Ventritex - Other)

All deaths occurred in patients whose defibrillators and lead systems were manufactured by Telectronics. This difference was highly significant (p=0.003) and does not appear to be

explained by a difference in left ventricular ejection fraction (EF) between patients receiving Telectronics, Medtronic and CPI defibrillators (Mean EF 46%, 47% and 55% respectively - p = NS). Although one of the deaths was probably related to sepsis following replacement of a broken transvenous lead there was no identifiable factor in the other three deaths which would seem to relate them to the use of a Telectronics system and it remains unclear why a clustering of deaths has occurred with this manufacturer's devices.

System Infection:

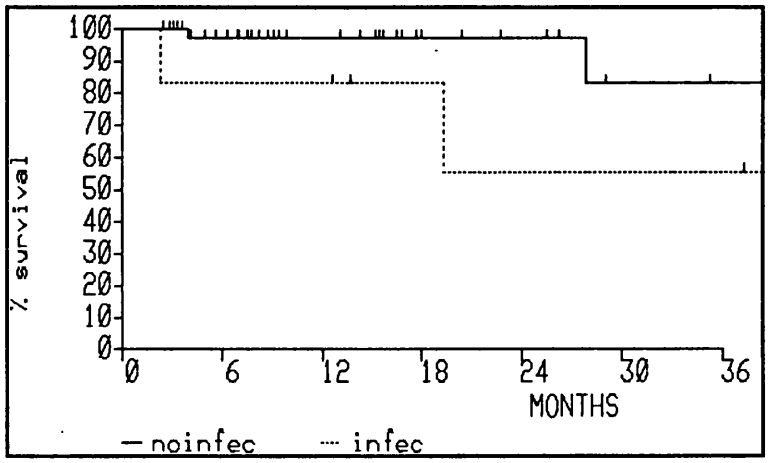

Figure 4.11: Survival stratified by presence (infec) or absence (noinfec) of in-hospital or late defibrillation system infection

Although the difference in survival fails to reach significance (Chi-squared = 3.04 p = 0.081) there is marked divergence of survival between patients who have an infected ICD system (either in hospital or later) and those who do not.

Other factors:

Implant procedure time and the occurrence of miscellaneous complications during hospitalisation were not shown to have any impact on subsequent mortality (p=NS).

Management Related Variables:

Antiarrhythmic drug therapy:

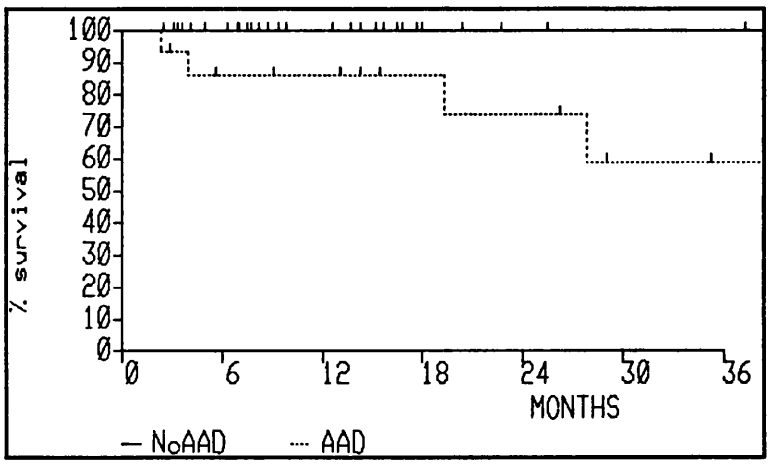

Figure 4.12: Survival stratified by continued antiarrhythmic drug use (AAD)

Mortality is significantly higher ($p<0.02$) in patients who require continued antiarrhythmic drug therapy (excluding ß-blockers). No difference was noted between ß-blocker and no-ß-blocker groups. Although there is a divergence in survival between those patients receiving ß-blockers and those who were not this fails to reach significance because of the relatively small proportion of patients (21%) who received ß-blockers in this study.

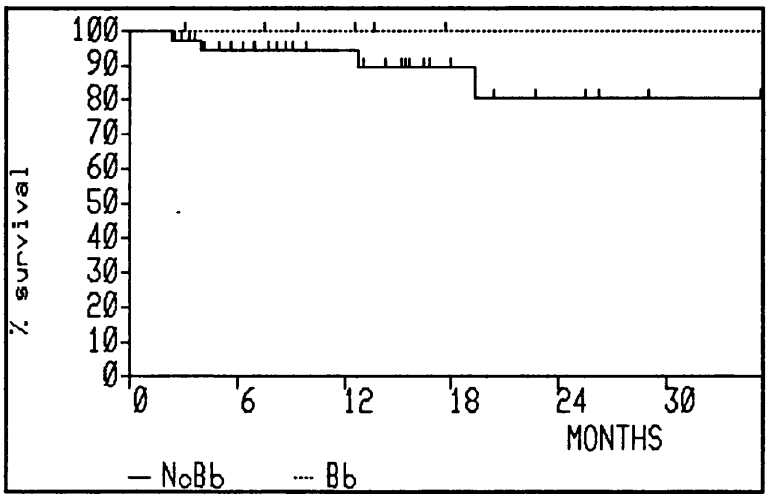

Figure 4.13: Survival in patients taking β-blockers (Bb) and those who were not (NoBb). This difference fails to reach significance (p=0.2)

Therapy Delivery:

There appears to be no difference in survival between patients who have and have not received a therapy from their ICD. The late divergence in the groups occurs when the numbers in each group are very small and fails to reach significance (p=NS).

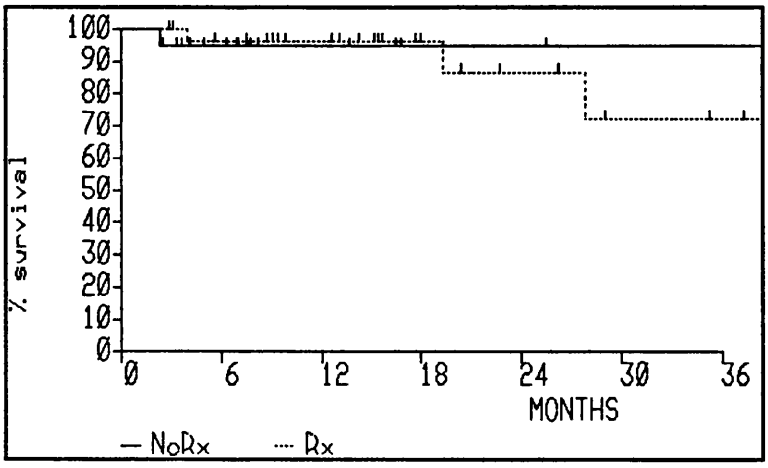

Figure 4.14: Survival stratified by presence (Rx) or absence (NoRx) of therapy from ICD

Device Programming:

Multilevel detection zone programming and the use of antitachycardia pacing and cardioversion therapies were not associated with increased mortality (p = NS).

Review of Variables associated with total survival:

Of the variables considered in this study four were significantly associated with impaired total survival by univariate analysis. These were left ventricular ejection fraction, poor functional status (NYHA grade 3/4), continued antiarrhythmic drug therapy and ICD manufactured by Telectronics. Two other variables (the presence of coronary artery disease and ICD system infection) approached statistical significance (p= 0.07 and p = 0.08 respectively). Of these six variables continued antiarrhythmic drug therapy, NYHA status and the presence of coronary artery disease were strongly associated with lower ejection fraction values whilst ICD manufactured by Telectronics and ICD infection were not. The relationship between these variables was examined using the Cox proportional hazards model.

The potential problems with the application of multivariate analytical techniques in populations where the number of cases is relatively small and the number of variables is large have already been alluded to in Chapter 3. Of these six variables the only one included by the Cox model was NYHA grade. NYHA grade has a risk ratio of 13.067 (Parameter estimate 2.57) and a Chi-square score of 12.9. No other variable significantly improved the fit of the model in this small population suggesting that left ventricular function reflected in functional capacity (NYHA grade) is the most important determinant of outcome in this population.

PATTERNS OF THERAPY DELIVERY:

Appropriate therapy delivery:

The cumulative incidence of appropriate therapy delivery in the population of 47 patients is shown in Figure 4.15.

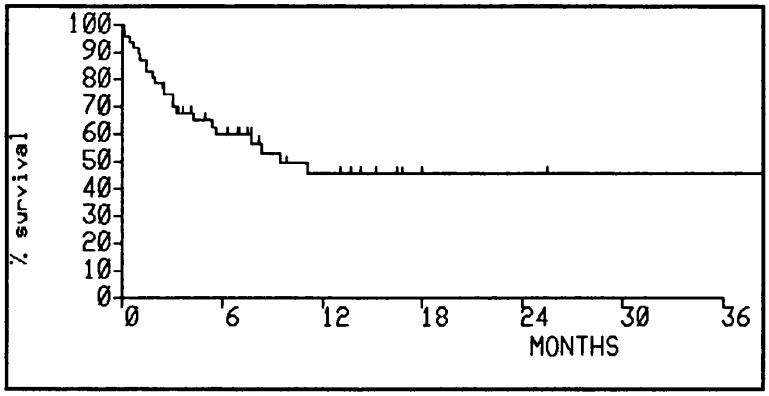

Figure 4.15: Cumulative incidence of appropriate ICD therapy delivery in 47 ICD recipients

Cumulative incidence of appropriate therapy delivery is 41% at 6 months, and 54% at 12 months remaining at this level out to 36 months.

ANALYSIS OF THE FACTORS ASSOCIATED WITH APPROPRIATE THERAPY DELIVERY:

Patient specific variables -

Age:

The mean age of patients receiving appropriate therapies was 47.9 years and 44.7 years in those who have not. This difference was not significant.

Ejection fraction:

There is a highly significant ($p<0.0001$) difference in ejection fraction between patients who received an appropriate therapy (Mean EF 36.9%) and those who did not (Mean EF 60.2%). This is clearly seen when an ejection fraction of 30% is used to dichotomise survival the population.

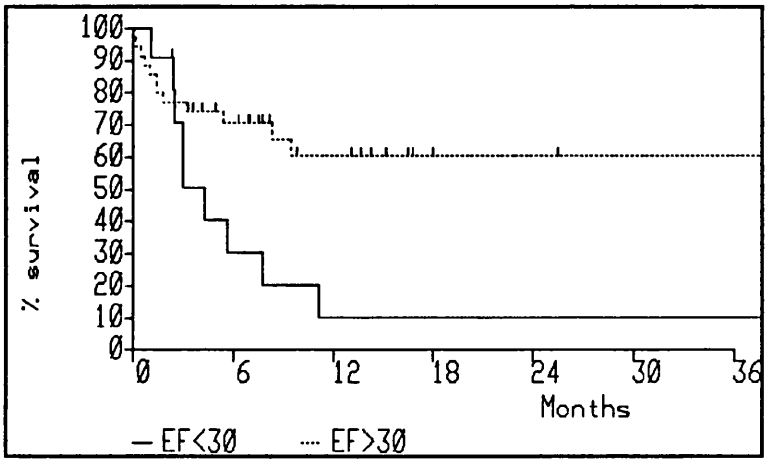

Figure 4.16: Survival free of appropriate ICD therapy delivery stratified by left ventricular ejection fraction.(EF>30) - LVEF greater than 30%. (EF<30) - LVEF less than or equal to 30%

Cumulative therapy delivery in the ≤30% EF group is 70% at six months rising to 90% at one year versus 31% at six months and 40% at one year for the EF>30% group.

Left Ventricular End Diastolic Dimension:

This variable also shows a significant difference between patients receiving therapy and those who do not ($p<0.01$). Mean LVEDD in patients who receive a therapy is 6.2cm versus 5.3cm in those who do not.

Heart Diameter on Chest X-ray:

Mean heart diameter on chest X-ray is 17.4cm in those who receive therapy versus 15.2cm in those who do not ($p<0.01$).

Clearly ejection fraction, LVEDD and heart diameter are not independent variables as is shown by the scatter diagrams below.

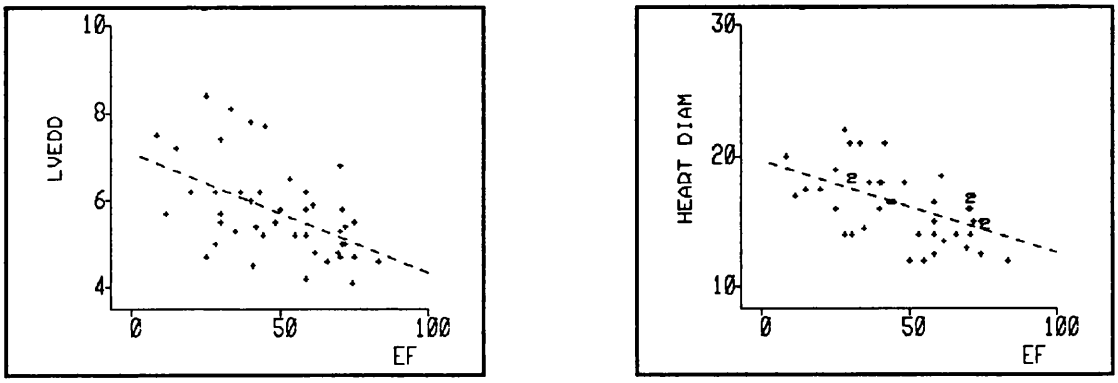

Figure 4.17: Scatter diagrams of left ventricular end-diastolic diameter (LVEDD) against ejection fraction (left) and heart diameter against ejection fraction (right)

Inducibility of arrhythmia at pre-implant Electrophysiology Study:

Patients with an inducible ventricular arrhythmia at pre-implant electrophysiological study are much more likely to receive an appropriate therapy (Chi-squared by Logrank test = 10.01, $p < 0.002$).

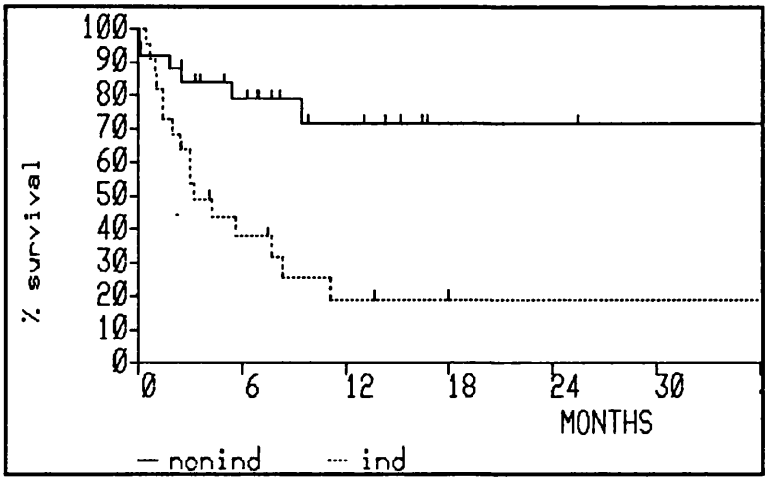

Figure 4.18: Survival free of appropriate ICD therapy delivery in patients with (ind) or without (nonind) inducible arrhythmia

Table 4.2: Cumulative probability of receiving an appropriate therapy stratified by results of pre-implant electrophysiology study

	Months since ICD implant			
	0	6	12	24
Noninducible at EPS	0	0.21	0.28	0.28
Inducible at EPS	0	0.62	0.81	0.81

However inducibility at electrophysiological study is strongly associated with ejection fraction (mean EF in inducible patients is 35.6 %, in noninducible patients 60.3%. $p < 0.001$). To see whether inducibility at electrophysiology study contributes any information over and above that which may be derived from the ejection fraction the population was divided into

high and low ejection fraction groups and the impact of further dividing the population based on inducibility was examined. In the low ejection fraction group only one patient was noninducible and therefore the comparison was not useful. However in the high ejection fraction group a clear pattern emerged.

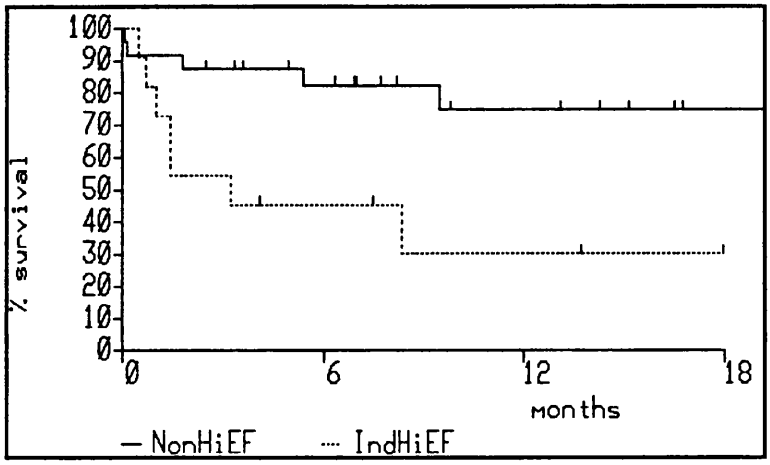

Figure 4.19: Survival free of appropriate ICD therapy delivery in patients with ejection fractions greater than 30% with (IndHiEF) or without (NonHiEF) inducible ventricular arrhythmia

Therapy delivery was statistically more likely to occur in the patients with inducible arrhythmias in this group (Logrank Chi-squared 6.39, $p<0.01$). However the distribution of ejection fractions within these two groups differs. The mean ejection fraction in the noninducible group is 61.6% versus 47.7% in the inducible patients so the difference in observed outcome could still be due to ejection fraction alone.

Patients who present with sustained ventricular tachycardia are significantly more likely to receive an appropriate therapy from their ICD (Chi-squared = 5.59, $p < 0.02$).

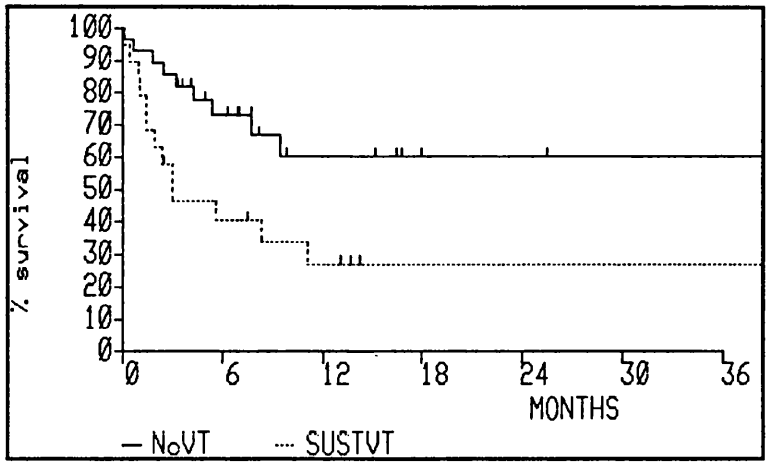

Figure 4.20: Survival free of appropriate ICD therapy delivery in patients who present with sustained ventricular tachycardia (SUSTVT) versus those who do not (NoVT)

Like inducibility this variable is strongly associated with ejection fraction. The mean ejection fraction in patients presenting with sustained ventricular tachycardia is 39.4% versus 55.2% for patients without sustained VT.

Implant Related Variables:

Epicardial and Transvenous defibrillation systems:

There was no significant difference between epicardial and transvenous systems in the occurrence of appropriate therapy delivery (Figure 4.21). Neither was there any difference with respect to any other implant related variables.

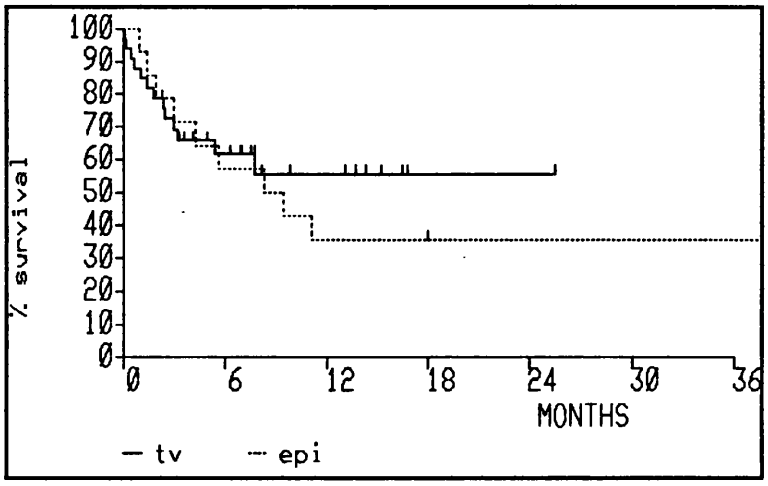

Figure 4.21: Survival free of appropriate therapy delivery stratified by defibrillator system type (tv = Transvenous, epi = Epicardial)

Management Related Variables:

Antiarrhythmic drugs:

Patients who continue to receive therapy with antiarrhythmic drugs (excluding ß-blockers) are more likely to receive an appropriate therapy from their ICD (Chi-squared 4.94, $p < 0.03$). There was no significant difference between patients who were and were not receiving ß-blocker therapy (Chi-squared 1.53, p = NS) although some divergence occurred when number were small at the end of the follow-up period (Figure 4.23).

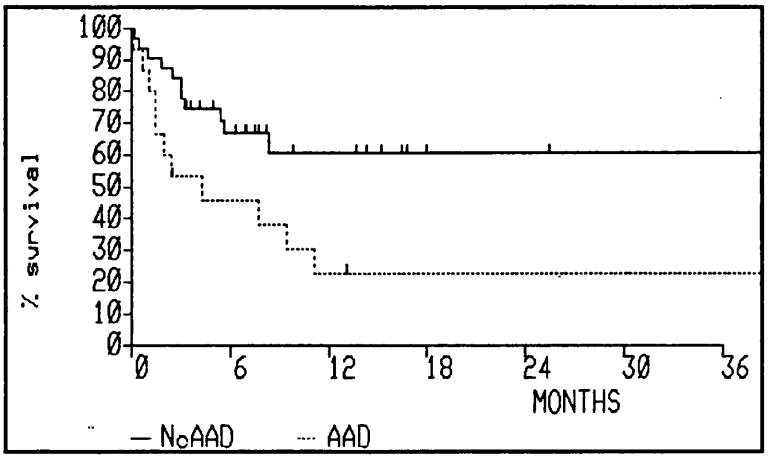

Figure 4.22: Survival free of appropriate ICD therapy delivery stratified by continued antiarrhythmic drug therapy (AAD) versus no antiarrhythmic drug therapy (NoAAD)

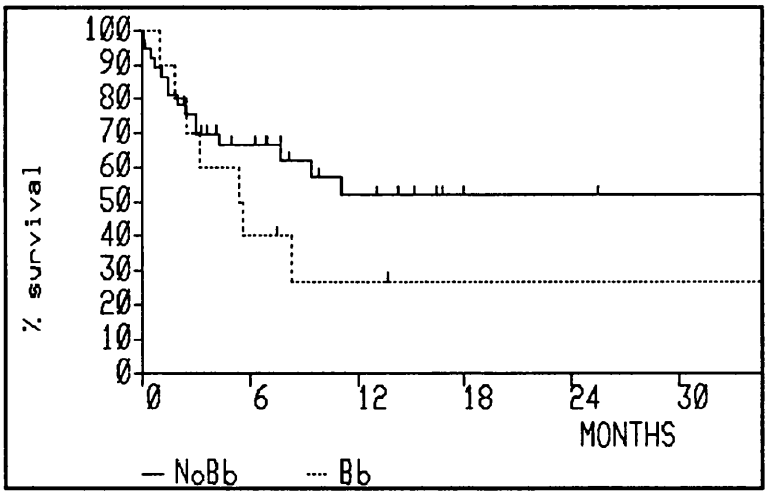

Figure 4.23: Survival free of appropriate ICD therapy delivery stratified by ß-blocker therapy (ßb)

Device Programming:

Patients who have two detection levels programmed are more likely than those with a single detection level to receive an appropriate therapy (Chi-squared = 10.74, p = 0.01). This difference is largely a reflection of that noted above as patients with an inducible arrhythmia are more likely to have a second detection level programmed to enable differing therapies to be selected for ventricular tachycardia and ventricular fibrillation. Usually this involves programming of cardioversion or antitachycardia pacing therapies for the slower arrhythmia. Mean ejection fraction in the group with two detection zones programmed is 35% compared with 57% in patients with a single therapy zone.

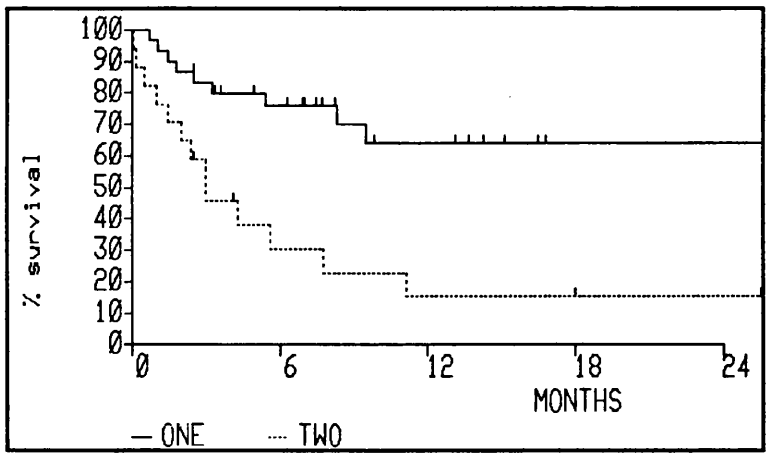

Figure 4.24: Survival free of appropriate ICD therapy delivery stratified by number of programmed detection zones

Review of Variables Associated with appropriate ICD therapy delivery:

Of the variables considered in this study seven showed a statistically significant association with appropriate ICD therapy delivery. These were left ventricular ejection fraction, left

ventricular end-diastolic diameter, heart diameter on postero-anterior chest X-ray, inducibility of ventricular arrhythmia at electrophysiological study, presentation with sustained ventricular tachycardia, continued antiarrhythmic drug therapy and multilevel detection zone programming. All of these variables showed a strong association with ejection fraction. Cox's proportional hazard model was used to examine these variables and to quantify the proportional hazard of therapy delivery associated with each percentage point fall in ejection fraction. Of the seven variables the Cox model selected left ventricular ejection fraction as the single variable best predicting the occurrence of appropriate therapy delivery. The relative risk (per 1% fall in ejection fraction) was 1.04 (chi-squared 11.69). Inclusion of any of the other variables (including inducibility of arrhythmia at electrophysiological study) failed to improve the "fit" of the model.

Patient Outcome After Appropriate ICD therapy delivery:

Few studies have examined what happens to patients after they have received their first appropriate therapy delivery. Figure 4.25 shows the distribution of therapy frequencies amongst our patients in the 12 months after delivery of the first therapy. For comparison Figure 4.26 shows the distribution of shock therapies during the same period. It is clear that after an initial period of activity most patients settle to receive less than one therapy every three months.

Figure 4.27 shows the incidence of unscheduled visits to the defibrillator clinic and hospital admissions over the 12 months after the first therapy delivery. In the three months after first therapy delivery 30% of patients make an unscheduled visit and hospital admission was required in 35% of patients for an average stay of 6.9 days. This was usually to allow

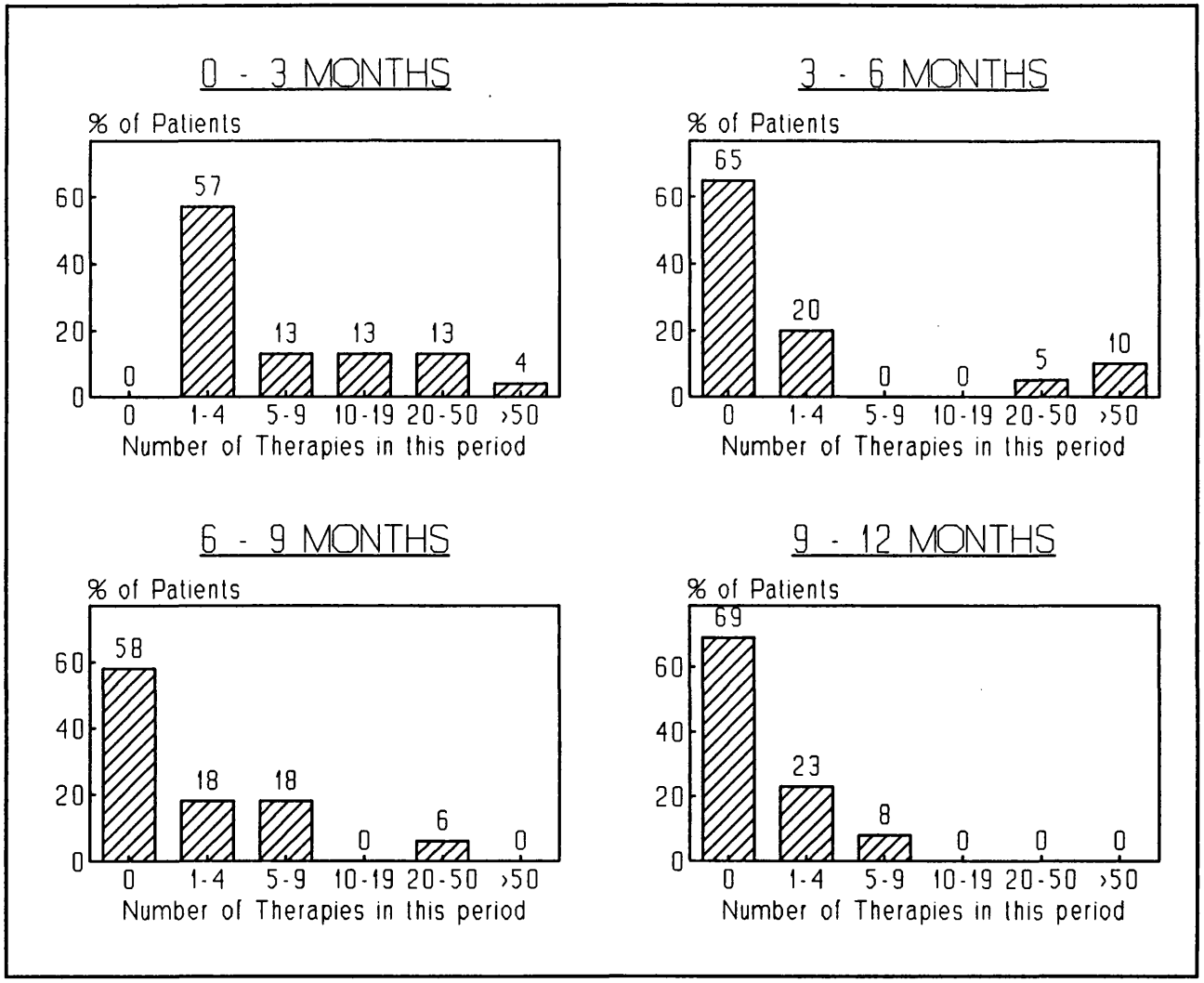

Figure 4.25: Occurrence of further therapies (pacing & shock) in subsequent three-month periods after first ICD therapy delivery.

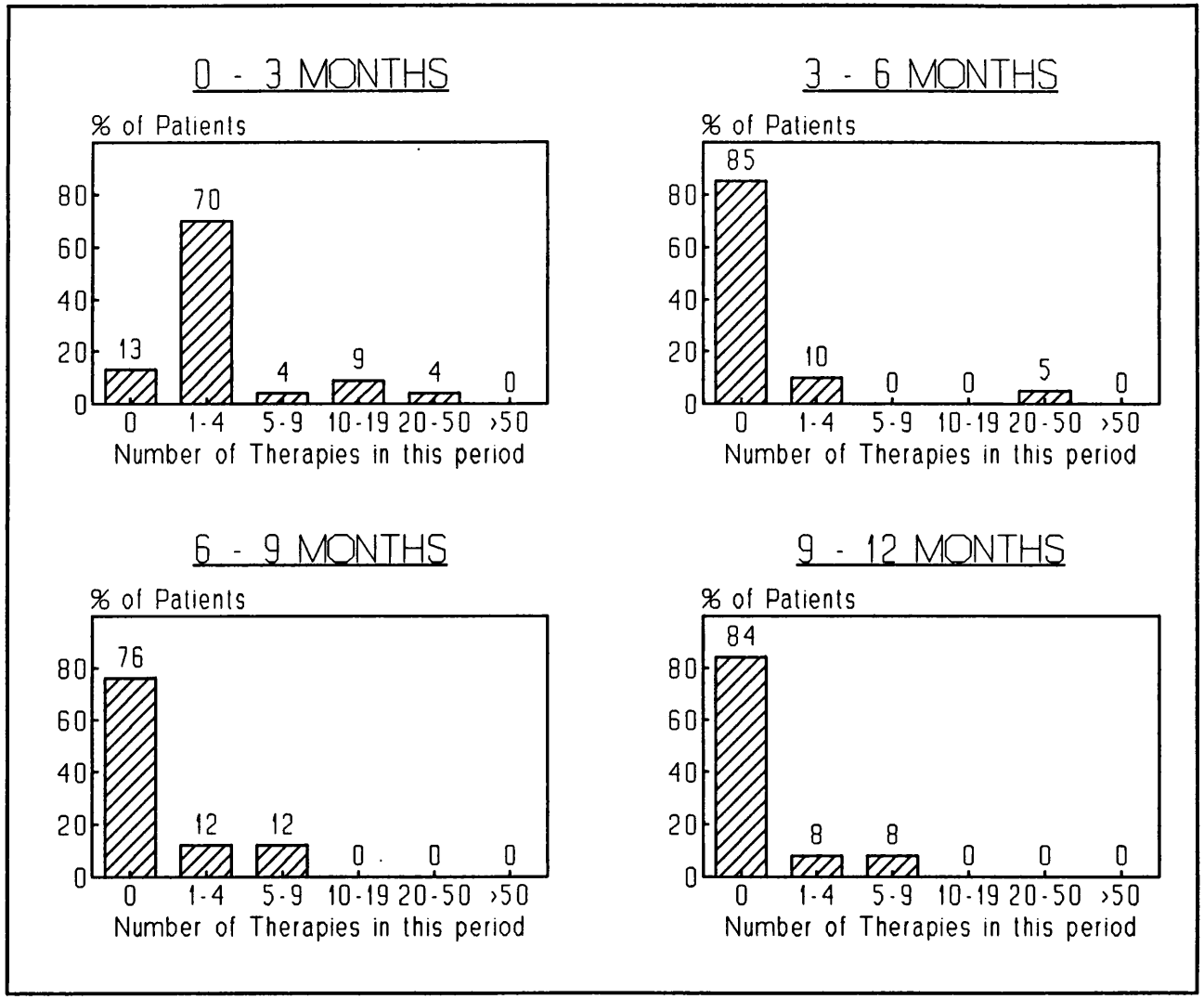

Figure 4.26: Occurrence of shock therapies in subsequent three-month periods after first ICD therapy delivery.

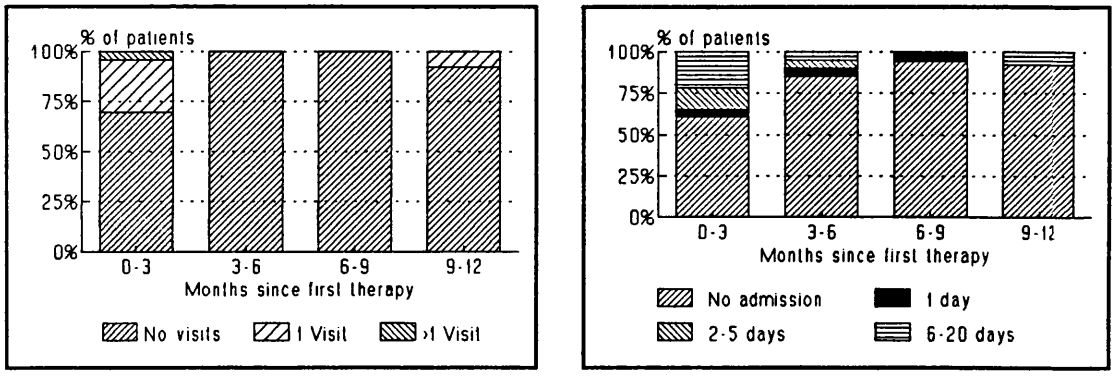

Figure 4.27: The incidence of unscheduled visits to the defibrillator clinic (Left) and of hospital admissions (Right) in the 12 months following first ICD therapy

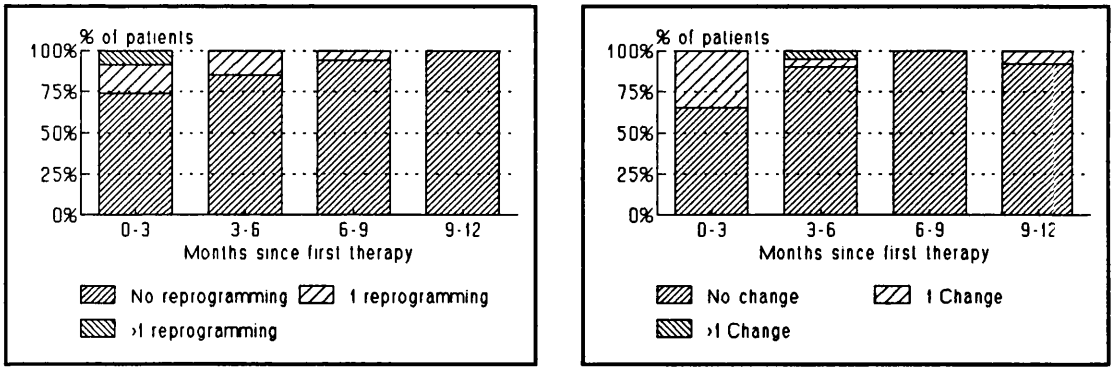

Figure 4.28: The incidence of ICD reprogramming (Left) and change in antiarrhythmic drug therapy (Right) in the 12 months after first ICD therapy delivery

control of very frequent episodes of ventricular arrhythmias or because appropriate therapies had triggered atrial fibrillation and subsequent inappropriate therapy. The incidence of unscheduled visits and of hospital admissions (excluding routine day case checks of defibrillator function) was below 10% for each subsequent three-month period. Thirty-five per cent of patients have a change or addition to their antiarrhythmic drug therapy (including

ß-blockers) after their first therapy episode (Figure 4.28). Reprogramming of the ICD was performed in 25% of patients in the three months after the first therapy, and in about 10% at 6 months and 5% at nine months (Figure 4.28). Hospital admission was required in 35% of patients and 20% were in hospital for over 6 days. This was usually to allow control of very frequent episodes of ventricular arrhythmias or because appropriate therapies had triggered atrial fibrillation and subsequent inappropriate therapy.

INAPPROPRIATE ICD THERAPY DELIVERY:

The cumulative incidence survival free of inappropriate therapy delivery in this population is 87% at 6 months, falling to 80% at 12 months and 71% at 24 months with this level persisting out to 48 months (Figure 4.29).

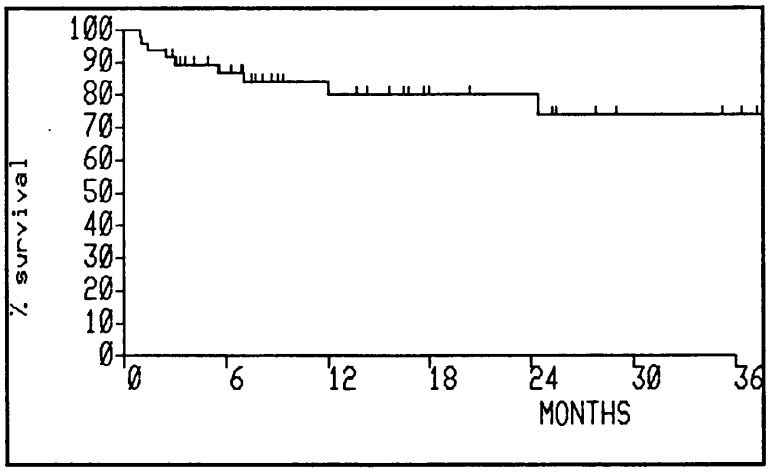

Figure 4.29: Cumulative survival free of inappropriate ICD therapy delivery

The occurrence of inappropriate therapies is a reflection of the inadequacies in the design of the current generation of implantable defibrillators which restricts their ability to identify ventricular arrhythmias with a high degree of specificity. Potential causes of inappropriate therapies include rapid atrial fibrillation, overlap of sinus tachycardia and ventricular

tachycardia rates, oversensing and hardware problems such as lead breaks. Amongst our 10 patients with inappropriate therapy delivery 6 had rapid atrial fibrillation, one had atrial tachycardia, one was due to sinus tachycardia and two to sensing electrode fractures. The low incidence of triggering due to sinus tachycardia reflects the careful programming of the device prior to discharge from hospital so that in all but one patient the detection rate for ventricular tachycardia was above the maximum which could be demonstrated during maximal treadmill exercise. In two cases with atrial fibrillation triggering inappropriate therapies the atrial fibrillation apparently resulted from the delivery of an appropriate therapy for a ventricular arrhythmia (although it is impossible to exclude the patient being in atrial fibrillation prior to delivery of the appropriate therapy). In view of the scale of inappropriate therapy delivery triggered by atrial fibrillation I have analysed the data to see if any variables were predictive of subsequent occurrence of atrial fibrillation and inappropriate therapy delivery.

Inappropriate ICD therapy delivery due to Atrial Fibrillation:

Univariate analysis was performed to see whether this outcome was related to a history of prior atrial fibrillation, left atrial size on echocardiography, delivery of appropriate therapies, or left ventricular ejection fraction.

History of prior Atrial Fibrillation:

Only four patients had a history of prior atrial fibrillation and there was no evidence that triggering of inappropriate therapies by atrial fibrillation was more common in these patients (Figure 4.30).

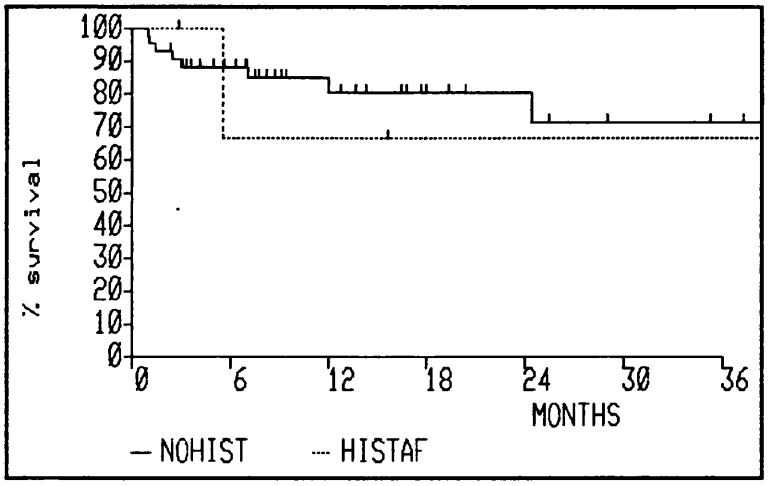

Figure 4.30: Survival free of inappropriate ICD therapy delivery in patients with (HISTAF) and without (NOHIST) a prior history of atrial fibrillation

Delivery of Appropriate Therapies:

A previous history of appropriate therapy delivery by the ICD had no impact on the incidence of inappropriate therapy delivery

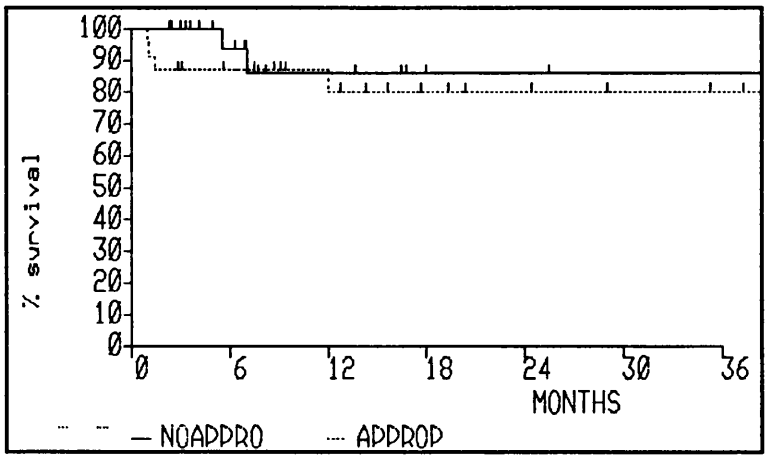

Figure 4.31: Survival free of inappropriate ICD therapy delivery in patients who have (APPROP) or have not (NOAPPRO) received an appropriate ICD therapy

Left Atrial Size:

Although the incidence of atrial fibrillation triggering inappropriate therapies appears higher in patients with left atrial diameter's greater than 4cm this difference does not reach statistical significance (Chi-squared = 1.13 p = NS).

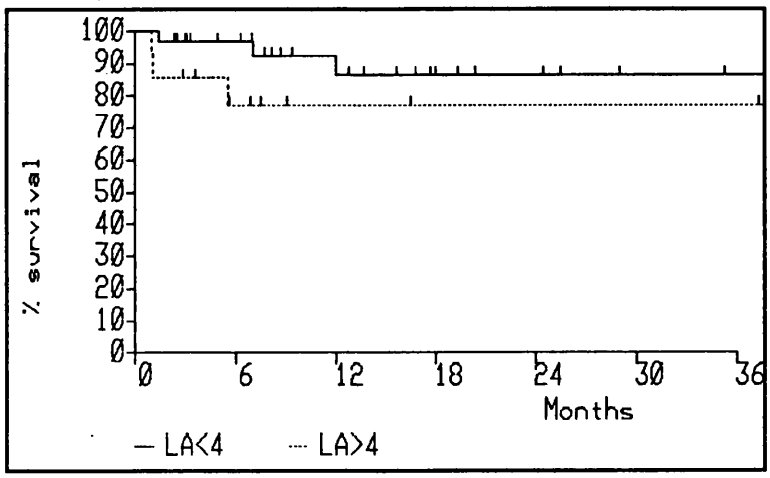

Figure 4.32: Survival free of inappropriate ICD therapy delivery stratified by left atrial size (LA<4 = left atrial diameter <4cm, LA>4 = left atrial diameter ≥4cm)

Left ventricular ejection fraction:

There appears to be a higher incidence of atrial fibrillation triggering inappropriate therapies in patients with ejection fraction of less than 30% but this also fails to reach statistical significance (Chi-squared 2.18 p=NS).

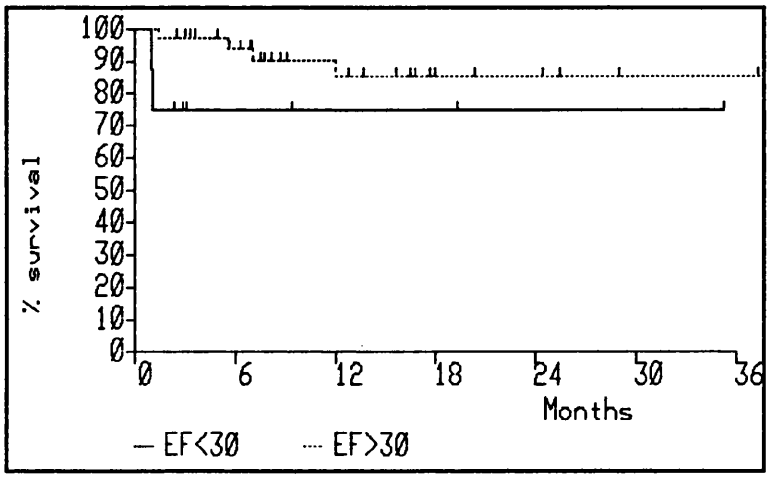

Figure 4.33: Cumulative survival free of inappropriate ICD therapy delivery in patients with an left ventricular ejection fraction of 30% or above (EF>30) versus patients whose ejection fraction is less than 30% (EF<30)

Patient outcome after inappropriate ICD therapy delivery:

Although inappropriate therapies have substantial nuisance value their overall impact on patients was low. Figure 4.34 shows the frequency and type of inappropriate therapies amongst the 10 patients affected. Figure 4.35 shows the action taken following these therapies. The hospital stays required were either to ensure control of atrial fibrillation or to revise the ICD system when lead breaks had occurred. Five of the ten patients required ICD reprogramming and five also required modifications of their antiarrhythmic drug therapy. No further hospital admissions, reprogramming or alterations of drug therapy were required after the first three months.

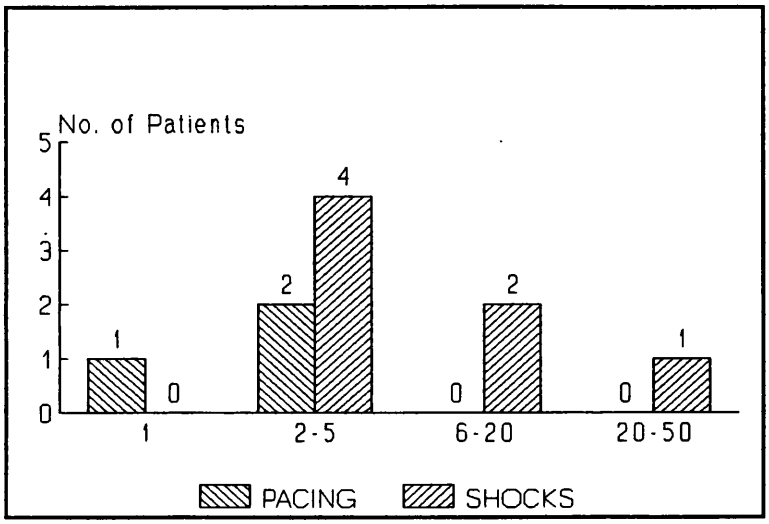

Figure 4.34: Frequency and type of inappropriate ICD therapy delivery

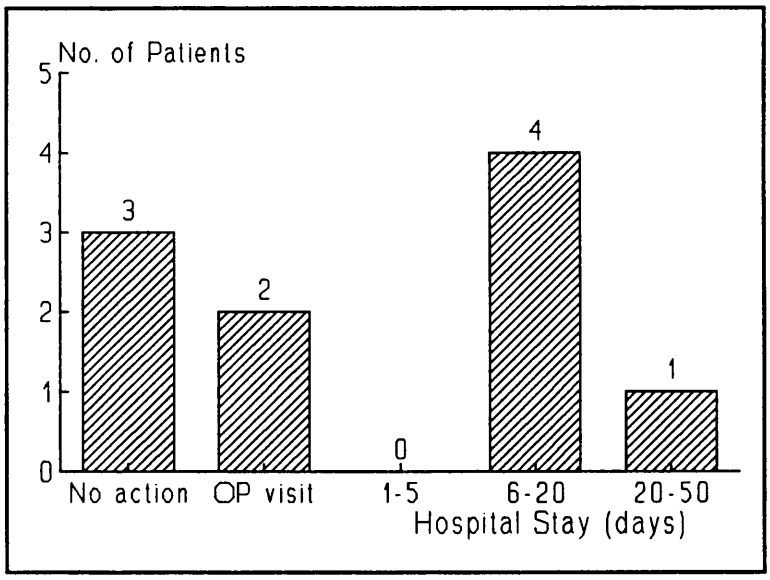

Figure 4.35: Action required after inappropriate ICD therapy delivery

Discussion:

The ICD and survival:

The limitations of existing studies of mortality reduction by the ICD have been extensively discussed in chapter 1 and in the introduction to this chapter. A definitive answer to the question of whether the ICD improves survival in patients at risk of sudden cardiac death must await the results of randomised prospective trials. However the more advanced data logging functions found on the third generation ICD used in this study enable the accurate classification of a large proportion of arrhythmia episodes. This enables us to perform a more sophisticated attempt at predicting hypothetical mortality in ICD recipients than that of Mirowski *et al.*(1983) and Gabry *et al.*(1987). The results of this analysis suggest that ICD use has increased total survival at 12 months from 73% to 95% and survival free of sudden cardiac death at 12 months from 77% to 100%. This strongly suggests that the ICD is achieving its aim of reducing mortality in this group of patients. Although there are potential objections to this type of hypothetical study one advantage is that the patients act as their own controls and there is no risk of ignoring confounding variables in the ICD versus no ICD groups.

Despite the use of the ICD four patients in our study died during the course of follow-up. One death occurred from progressive hypotension and systemic infection two months after ICD implant, one during cardiac transplant for worsening left ventricular function and frequent episodes of ventricular tachycardia and two during "arrhythmia storms" when increasingly frequent ventricular arrhythmias could not be controlled by drug therapy. One of these patients had had their ICD removed as a result of infection, although the epicardial patches remained in situ. The results of this study concur with many others which show that low ejection fraction and poor functional status (NYHA grade) are associated with higher

subsequent mortality. Interestingly heart diameter on chest X-ray which emerged as the most significant factor in deciding the success or failure of attempted transvenous implantation did not emerge as a significant factor for subsequent survival. Whilst cardiac bulk may have a direct impact on the defibrillation thresholds achieved at device implant measures of cardiac function, such as the ejection fraction, seem to be more important in determining subsequent survival. This study does not support the findings of Zilo *et al.*(1991) that the occurrence of ICD shock itself is a predictor of subsequent mortality. Equally there was no evidence that presentation with sustained ventricular tachycardia was a significant risk factor for subsequent mortality as suggested by Edel *et al.*(1992). In both Zilo and Edel's studies the two groups being compared were not matched for ejection fraction and it is likely that differences in ejection fraction explain the observed differences in survival. Only two patients in this study underwent coronary artery bypass grafting so it was impossible to confirm or refute Levine's observation (Levine *et al.* 1991) that coronary artery bypass grafting is associated with reduced mortality. Our study failed to show any difference in mortality between epicardial and transvenous lead implantation. Transvenous lead implantation has been reported to be associated with an implant mortality of around 1% compared with 3% for epicardial implantation (Nisam *et al.* 1991b). Such a difference is too small to be observed in a study of this size. The limited multivariate analysis which it was possible to perform on such a small number of patients confirmed the finding that cardiac function (assessed by left ventricular ejection fraction) or functional status (assessed by NYHA grade) appeared to be the most important variable in determining subsequent survival after ICD insertion. The significant association of mortality with devices from a single manufacturer by univariate analysis is likely to be a spurious finding. It has not been replicated in other studies and in only one of our four deaths could problems with the ICD be directly implicated in the death.

The ICD and Appropriate Therapy Delivery:

In this study 41% of patients had received an appropriate therapy delivery by 6 months rising to 54% at 12 months. This figure is broadly comparable with that noted in other studies. Left ventricular ejection fraction was again a powerful predictor of appropriate therapy delivery. In patients with an ejection fraction of 30% or less cumulative incidence of therapy delivery at 6 months is 70% rising to 90% at 12 months. In the >30% group only 31% have received an appropriate therapy at 6 months rising to 40% at 12 months. Larger values for left ventricular end-diastolic diameter and heart diameter on chest X-ray were also associated with a higher incidence of therapy delivery but these variables are strongly associated with ejection fraction. The presence of inducible arrhythmia at pre ICD implant electrophysiology study was another variable powerfully associated with subsequent appropriate therapy delivery. Patients with inducible ventricular tachycardia had an 81% chance of receiving an appropriate therapy at 12 months whilst in those with no inducible arrhythmia the incidence of appropriate therapy delivery was just 28%. This observation is confounded by the finding that the ejection fraction in the inducible group is 35.6% versus 60.3% in the noninducible group. In the Cox proportional hazard model inducibility of arrhythmia was not found to provide significant additional predictive information over and above that derived from the ejection fraction alone. However inducibility may be of additional value within the high ejection fraction group. A larger study would be required to confirm this observation. The finding that ejection fraction and inducibility in combination are powerful predictors of recurrent cardiac arrest has previously been reported by Wilber *et al.*(1988) in cardiac arrest survivors. In this study ejection fraction was dichotomised at 30% and inducibility of arrhythmia appeared to confer additional information in predicting subsequent recurrence of cardiac arrest. However the possible confounding effects of differing ejection fraction distributions within the inducible and noninducible groups was not considered.

Continued antiarrhythmic drug therapy is associated with a higher incidence of appropriate therapy delivery probably reflecting a tendency to continue the use of antiarrhythmic drugs in patients with a higher frequency of arrhythmia episodes prior to ICD insertion. We were unable to replicate the findings of Levine *et al.*(1992) that ß-blocker therapy was associated with a lower incidence of therapy delivery and in our population the trend was to a higher incidence of therapy delivery in the ß-blocker treated group. In summary the major factor associated with the subsequent occurrence of arrhythmias and delivery of appropriate ICD therapies appears to be the left ventricular ejection fraction with a possible subsidiary association for inducibility of arrhythmias at electrophysiological study. Analysis of outcome after delivery of appropriate therapy indicates that about a third of patients require reprogramming or a change in drug therapy and a small proportion of patients require hospital admission (usually due to very frequent occurrence of further episodes after the initial therapy delivery). The medical input required for patients receiving appropriate therapies is small compared with that which would be required for arrhythmic episodes in the absence of the ICD. In each three-month period following the first delivery of an appropriate therapy about a third of patients receive a further device therapy.

The ICD and Inappropriate Therapy Delivery:

The incidence of inappropriate therapies in patients receiving an ICD remains a source of concern. This problem has received relatively little attention although its potential seriousness is well recognised (Johnson & Marchlinski 1991). In this population the incidence was 20% at 12 months rising to 29% at 24 months. Seven of the 10 episodes of inappropriate therapy delivery were due to atrial fibrillation but only one of these episodes occurred in a patient with a prior history of atrial fibrillation. Inappropriate therapies due to atrial fibrillation can be particularly troublesome as the variable rate can lead to multiple redetections of the

arrhythmia by the ICD triggering large number of shock therapies. Two of the patients in this study received more than 10 shocks within a few hours of their first inappropriate therapy. Univariate analysis failed to identify any single variable which predicted the occurrence of subsequent atrial fibrillation triggering inappropriate therapy delivery although low ejection fraction and larger left atrial diameter both showed a trend towards a higher incidence of subsequent atrial fibrillation. A larger study population would be required to confirm these observations. Follow-up of patients who had received inappropriate therapies showed that no patient had further problems with inappropriate therapy delivery in the 12 months following the initial episode. Generally altering drug therapy and reprogramming the device would usually alleviate the problem.

Conclusions:

Although our study population has a different composition from that of other published series of ICD patients the cumulative incidence of appropriate therapy delivery is similar. The use of a large proportion of third generation ICDs has enabled a reasonable attempt to be made at assessing the mortality in the absence of device therapy and the figures suggest a substantial reduction in total and sudden cardiac death mortality due to the use of the device. Additionally patients who are rescued from arrhythmic death by the device seem to gain significant benefit as they have not shown a high mortality from other causes. Non sudden death mortality after ICD insertion appears strongly related to cardiac function, expressed either as left ventricular ejection fraction or New York Heart Association grade. That other factors have been reported to be important in other studies is probably due to a the confounding effect of differing ejection fractions. The occurrence of appropriate therapy delivery is also predicted by poor cardiac function and inducibility of ventricular tachycardia

at electrophysiological study may be an additional predictive variable. Inappropriate therapy delivery remains a significant problem, even with third generation ICD and is most commonly due to atrial fibrillation. In our small study no variable was found to be predictive of inappropriate therapy delivery. New predictive variables or combinations of variables must be identified if we are to improve the selection of patients to receive ICD therapy.

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CHAPTER 5:

A STUDY OF THE LONG-TERM PERFORMANCE AND COMPLICATIONS ASSOCIATED WITH THE USE OF TRANSVENOUS DEFIBRILLATION LEAD SYSTEMS:

Introduction:

The past decade has seen a period of rapid development in the field of defibrillation lead systems. The pattern of development is similar to that which occurred with pacemaker electrodes in the 1960's and 1970's. Initial use of epicardial lead systems gradually gave way to endocardial electrodes as the long-term performance and complication rate with these leads were lower. The history of transvenous defibrillation electrode systems has been described in Chapter 2. Since they were first used in 1986 they have undergone extensive development and all six manufacturers of implantable defibrillators have a transvenous lead system under evaluation. When this study commenced in 1989 all of the available transvenous lead systems were investigational devices and their performance and the complications associated with their use were essentially unknown. In this part of the thesis our experience with these lead systems will be reviewed and their performance compared with that of epicardial lead systems.

Measures of system performance:

Because of the complexity of the ICD there are a number of aspects to be considered when assessing the long-term performance of these devices.

The primary measures of system performance are:

- Stable pacing threshold
- Stable sensing performance
- Stable defibrillation threshold
- System longevity
- Morbidity and mortality associated with system use

Each of these measures must be optimised if the ICD is to realise its potential as a long-term therapy for serious ventricular arrhythmias.

Performance of Epicardial Defibrillation Systems:

Because epicardial defibrillation systems have been available for 13 years there is a considerable body of data on their performance.

The limitations of chronic epicardial pacing particularly with respect to rising chronic pacing thresholds are well known (Oldershaw *et al.* 1982). However, few of the many published series have described the chronic pacing and sensing performance of epicardial pace sense electrodes used with ICDs. Shepard *et al.*(1992) compared the pacing threshold and R-wave amplitude at ICD implant with that found at ICD generator replacement (on average at 27 months). Acute pacing threshold was 4.5 ± 2.2 Volts at 0.5ms and chronic threshold was 3.8 ± 2.1 Volts at 0.5ms. Acute R-wave amplitude was 12 ± 5.9 millivolts and chronic R-wave amplitude 13 ± 8.5 millivolts. Although there was no evidence of a chronic rise in pacing threshold in this study only seven patients were involved and the initial pacing thresholds were high.

That defibrillation thresholds do not rise dramatically in patients with epicardial patch electrodes is strongly suggested by the continued clinical efficacy and low sudden death mortality in ICD recipients. Animal studies have suggested that there is no significant change

in defibrillation threshold in the 12 weeks after epicardial patch electrode implantation (Kallok *et al.* 1986). Experience in man comes largely from findings at elective ICD generator replacement. The most comprehensive data comes from a study published by Frame and colleagues (Frame *et al.* 1992) of 31 recipients of epicardial defibrillation systems who underwent at least one system revision. Their defibrillation thresholds at successive system replacement are shown in Figure 5.1.

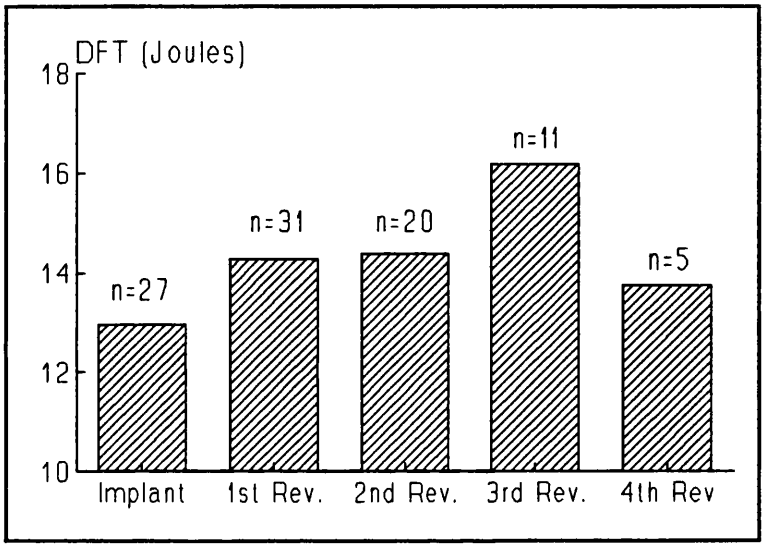

Figure 5.1: Long-term stability of epicardial patch defibrillation thresholds at system revision (from Frame et al. 1992)

Although there was a trend towards a rise in defibrillation thresholds with time this failed to reach statistical significance. Additional evidence for stability of defibrillation thresholds over time comes from two other studies. Guarnieri *et al.*(1987) demonstrated a rise in defibrillation threshold from 12.7 joules at device implant to 16.9 joules at device replacement. However this rise was accounted for solely by a striking rise in the defibrillation threshold in the subgroup of patients receiving Amiodarone therapy. In the remaining 12 patients there was no change in the defibrillation threshold. These findings were replicated

in a study comparing defibrillation thresholds at generator replacement in patients randomly allocated to therapy with mexiletine or amiodarone (Jung *et al.* 1992). Thresholds in the Amiodarone group rose from 14.1 to 20.9 joules whilst in the mexiletine group the defibrillation threshold was 14.5 joules at implant versus 14.8 joules at device replacement. The large volume of data on defibrillation threshold at device replacement which should be available in individual manufacturers databases has yet to be published.

There is as yet no systematic data available on the longevity of individual lead systems. By contrast, the longevity of ICD generators has been extensively documented (Bilitch *et al.* 1988, Moore *et al.* 1990, Song *et al.* 1992). This feature is of course common to both epicardial and transvenous lead systems. It is clear that the longevity of ICD generators is steadily increasing (Figure 5.2).

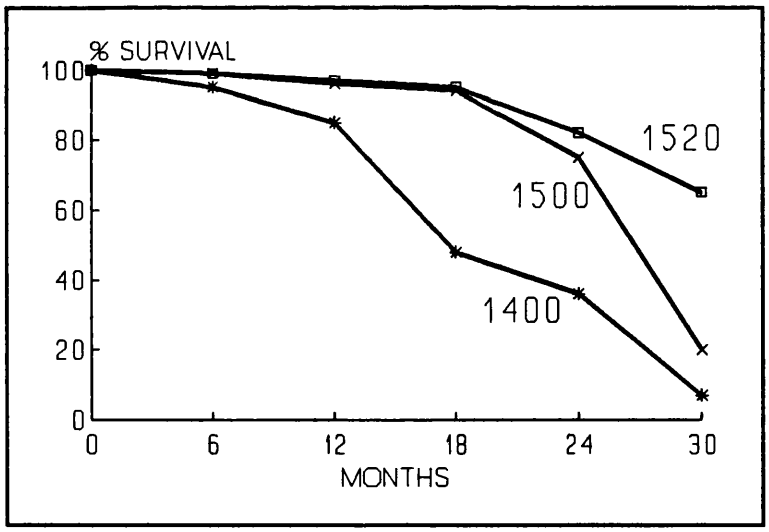

Figure 5.2: Longevity of three series of implantable defibrillator manufactured by CPI (Cardiac Pacemakers Inc.). The more recent version (1520 series) shows improved longevity over the earlier 1400 and 1550 series (data from Moore et al. 1990)

Morbidity and Mortality of Epicardial System Implantation:

Nisam *et al.*(1991b) reviewed the results for 1,030 patients published in several series. The overall mortality in these patients was 2.4% with a range of 1.2 - 4.4%. Perioperative mortality appears to be higher when ICD implantation is combined with coronary artery bypass grafting (Alfieri *et al.* 1992) or with other cardiac surgical procedures (Edel *et al.* 1992) and in patients who have had a previous unsuccessful attempt at implantation of a transvenous ICD system perioperative mortality may approach 10% (Lindemans *et al.* 1991). The majority of perioperative deaths have been due to the occurrence of incessant arrhythmias or progressive cardiac failure (Edel *et al.* 1992). It is unclear how much of the implant mortality associated with epicardial patch placement is related to the patches themselves and how much to the surgical procedure. Nonetheless new ways of placing epicardial patches such as the use of thoracoscopic techniques are still being actively investigated (Goodman *et al.* 1992).

Early postoperative complications (<30 days from implant) occur in between 6 and 30% of patients (Nisam *et al.* 1991b) but the majority of these have been of minor significance such as pleural effusion and atelectasis. Infection of the ICD system remains the most significant problem and has been reported in between 3 and 7% of patients (Bakker *et al.* 1992) requiring removal of the system in around 3% of patients. Electrode related problems due to insulation breakage, electrode fracture, migration or patch crinkling can occur in 5 to 8% of patients.

In summary epicardial defibrillation systems maintain their long-term performance well, albeit with some rise in pacing threshold. There may also be a slow chronic rise in defibrillation thresholds, exacerbated in the presence of amiodarone. Epicardial system implantation is associated with a mortality of around 4% and around 10% of patients suffer morbidity due to infection or electrode related problems.

Performance of endocardial (transvenous) defibrillation systems:

Most published studies of endocardial lead performance have concentrated on defibrillation thresholds at system implant with little reference to the pacing and sensing performance of the leads. The lack of reporting of this aspect of performance suggests that no problem has been encountered. However, one area of particular interest has been the impact of transvenous catheter shock delivery on pacing threshold and R-wave amplitudes. As early as 1984 it was realised that there could be problems when a defibrillating shock was delivered through electrodes which were also used for pacing (Yee *et al.* 1984). The authors noted a rise in pacing threshold from 1.4 to 2.4 volts and loss of R-wave amplitude from 5.9 to 3.4 millivolts with a return to control values over a 10 minute period. This observation has been repeated at the time of lead implantation with the CPI Endotak™ system (Kühlkamp *et al.* 1991, Isbruch *et al.* 1991) and the Telectronics EnGuard™ system (Accorti *et al.* 1992). No clinical sequelae of this observation have been reported.

In our study three patients were unable to proceed to transvenous lead implantation because of difficulty in obtaining satisfactory pacing thresholds or R-wave in the right ventricle. This very high incidence is without parallel in published studies although a 1.5% incidence of failure to obtain an adequate position of the lead in the right ventricle was reported in the CPI Endotak™ study (Hauser *et al.* 1992).

Morbidity and Mortality Associated with Transvenous System Implantation:

Because these system have been available for a shorter time there is much less information on their overall performance than for epicardial systems. Comparison of their performance with that of epicardial systems is difficult because randomised comparison of the two approaches has not been performed and historical comparisons with epicardial implants are

confounded because of probable changes in the type of patient being referred for ICD implantation. The closest approximation to a study of this type is that published by the worldwide PCD investigators comparing mortality of the two approaches on an intention-to-treat analysis (Lehmann *et al.* 1992). This showed an overall mortality for epicardial patch implants of 4.7% compared with 1.6% for transvenous implants ($p<0.001$). The implant mortality for those patients who actually received a transvenous system was just 0.3%. However, in those patients in whom transvenous implantation proved impossible the mortality associated with subsequent epicardial system implant was 8%.

The use of transvenous electrode systems clearly avoids the morbidity associated with thoracotomy. In a series of 64 patients ten had problems with haematoma associated with a subcutaneous patch but all of these patients were anticoagulated, one had a floating right atrial thrombus, one a subclavian vein thrombosis and one a system infection leading to device explant (Block *et al.* 1992). Reports of lead system performance for the Endotak™ and Transvene™ lead systems are available. In 302 patients receiving the Endotak™ lead system four lead displacements and one right ventricular perforation have been reported (Hauser *et al.* 1992). Four patients did not receive the lead system because of difficulty positioning the lead within the right ventricle mirroring our own experience with difficulty obtaining satisfactory pacing or sensing in some patients (see Chapter 3, Page 67). General complications were not discussed in this study. With the Medtronic Transvene™ system two right ventricular lead displacements occurred in 103 patients receiving the system (Lindemans *et al.* 1991). Displacement of three leads positioned in the superior vena cava and three leads in the coronary sinus occurred in the same population. A subclavian crush lead fracture was also reported in this group and three pocket haematomas occurred. Pocket seromas were reported in five patients in this study. Defibrillator "twiddling" with breakage of a defibrillation electrode has also been reported for an epicardial system where the ICD generator was mobile within its pocket (Mehta *et al.* 1992).

Patients and Methods:

The 48 patients described in Chapter 2 form the population for the analyses of ICD implant success, patient survival and therapy delivery which is the core of this thesis. The analysis of lead system performance is based on 35 transvenous implants in 33 patients (data from two complete system replacements with the Medtronic Transvene™ system is included) and 14 epicardial implants in 14 patients. The lead systems used are described in detail in Chapter 2 (Page 46) and the numbers of each type used are summarised in Table 2.2 (Page 50). The data for the three Telectronics DF lead systems and four Telectronics EnGuard™ systems implanted have been pooled and collectively described as data from the EnGuard™ system as these leads are identical except for a modification in the method of manufacture. Data is available for system performance at implant, prior to hospital discharge, at 1 month, 3 months and 3-monthly thereafter. Compliance with this schedule exceeds 97%. Data collection for this section of the study is complete to January 15th 1993.

The long-term comparison of pacing thresholds between different lead systems is restricted by differences in the way which the threshold is measured between different ICD generators. Some generators use a voltage threshold at a fixed pulse duration whilst others use a pulse width threshold at a fixed voltage. For each individual lead system/ICD generator combination the same method has been used throughout this study. To enable longitudinal comparisons of pacing threshold the different pacing thresholds have been converted to energy thresholds (in microjoules) based on an assumed lead impedance of 500 ohms to enable relative comparisons to be made. It should be stressed that such thresholds do not enable direct comparison between different lead systems. To do this comparison of the chronaxie and rheobase are required and this is beyond the capability of the limited threshold measuring facilities incorporated in current ICDs. For longitudinal studies of pacing performance energy thresholds have also been expressed as a percentage of that noted at

lead implant. Sensed R-wave amplitudes have all been compared in millivolts. Data is not available for all patients because some of the more basic ICD's offer no means of assessing the pacing threshold and surprisingly some of the most modern devices do not allow measurement of R-wave amplitude or pacing lead impedance.

The longitudinal assessment of defibrillation efficacy posed a number of problems. When this study was conceived there was concern about the safety of repeated testing of defibrillation thresholds (see Chapter 3, page 60) and it was decided not to formally evaluate the long-term defibrillation performance of epicardial defibrillation systems as there was already considerable evidence of their efficacy. However because of the novelty of transvenous defibrillation systems regular evaluation was deemed necessary. All patients with a transvenous defibrillation system had a check of defibrillation function prior to discharge from hospital and subsequently at the 1 or 3 month visit, and annually thereafter. The extent of this testing was limited compared to that at implant, in part because this testing was performed under sedation rather than general anaesthesia. An attempt was made to achieve defibrillation with a 20 joule shock. If this was successful no further testing was undertaken. If this failed a 34 joule shock was delivered. The prime objective was to minimise the number of fibrillation inductions involved. Prior to hospital discharge a first shock energy of 34 joules was often chosen and step down testing was not attempted. This was also the case in a few patients where the defibrillation safety margin had been marginal at implant or where defibrillation testing had been problematic due to difficulty with induction of ventricular fibrillation. The conclusions which can be drawn from such testing are necessarily limited but we have analysed the data on the basis of whether a 20 joule shock was successful at each successive follow-up and whether a 34 joule shock was successful if this failed.

All complications associated with ICD use have been recorded for both transvenous and epicardial implants. Recording of complications has been divided into early (<30 days) and

late (>30 days) periods. The overall survival of the ICD system as distinct from that of the patient has also been analysed.

Analysis of data has been performed using the unpaired t-test, Mann-Whitney U test, Chi-squared test and the Logrank test.

Performance of Implanted Defibrillation Systems:

Pacing & Sensing:

Epicardial systems -

Generally good R-wave amplitudes were obtained at epicardial system implantation. An area of relatively normal myocardium was selected for insertion of the screw-in electrodes. One patient had consistently poor signal amplitudes requiring insertion of an endocardial pacing lead for adequate sensing. The chronic R-wave amplitude of the epicardial leads for individual patients is shown in Figure 5.3 and the population values in Figure 5.4. In Figure 5.4 the R-wave is also shown as a percentage of the individual patient's value at the previous visit which removes spurious variation due to the differing number of patients who have completed each follow-up period.

The fall in amplitude of the R-wave from implant to pre-discharge is statistically significant ($p<0.05$) but in part may reflect differences between measurements made with the external pacing systems analyser and those made by the ICD. In particular the ability of the ICD's used in this study to measure R-wave amplitude is limited and relies on adjusting the input sensitivity in discrete steps to find the level at which sensing failure occurs. In many patients sensing continues satisfactorily even at the lowest programmable sensitivity so that

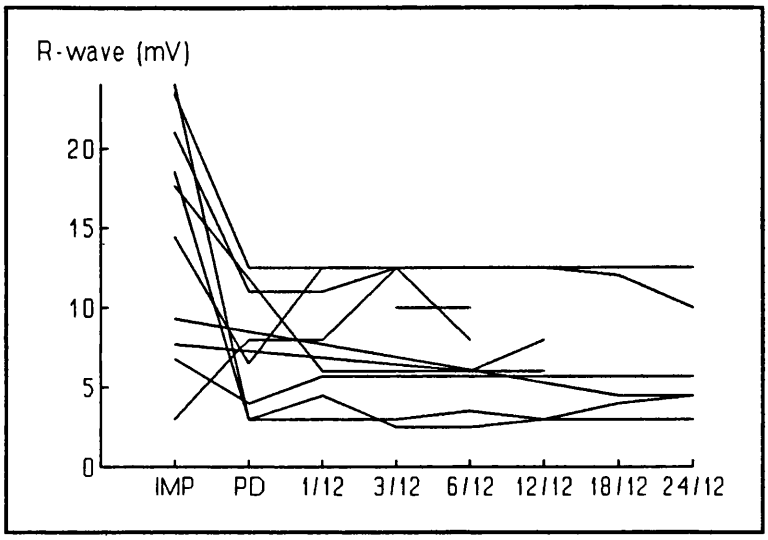

Figure 5.3: R-wave amplitudes for individual patients with epicardial lead systems at implant (IMP), pre-discharge (PD) and at 3 to 24 months

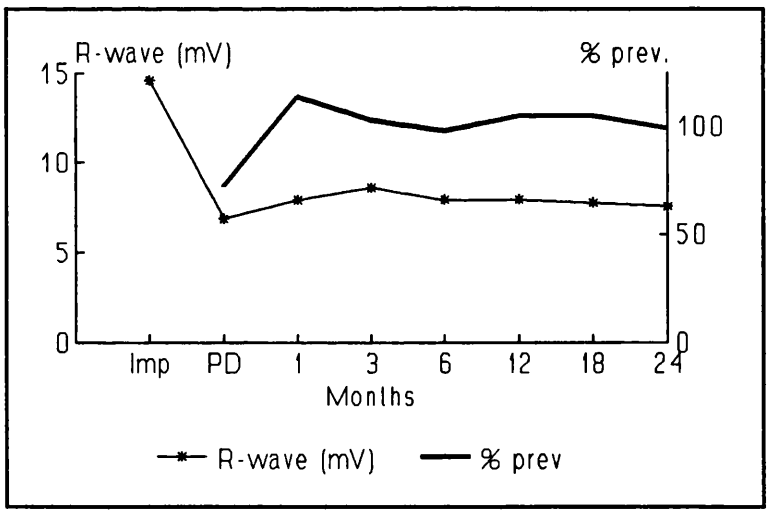

Figure 5.4: Mean R-wave amplitude and percentage of R-wave at previous visit for patients with epicardial lead systems

an exact measurement of R-wave amplitude may not be made. Filtering circuitry within the ICD sensing circuit may also have an impact on the amplitude of the measured R-wave.

These figures indicate that there is no significant change in R-wave amplitude from the pre-hospital discharge check throughout the rest of the study. The chronic pacing thresholds for the epicardial lead systems are shown in Figures 5.5 and 5.6.

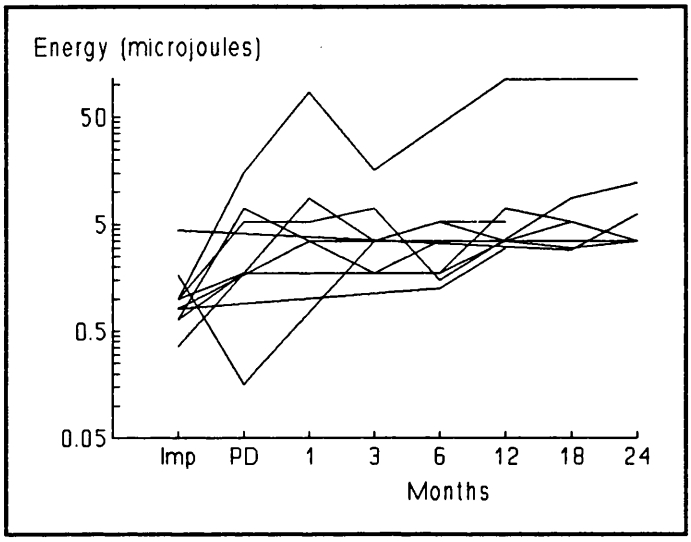

Figure 5.5: Chronic pacing thresholds for the 13 patients with epicardial sensing leads

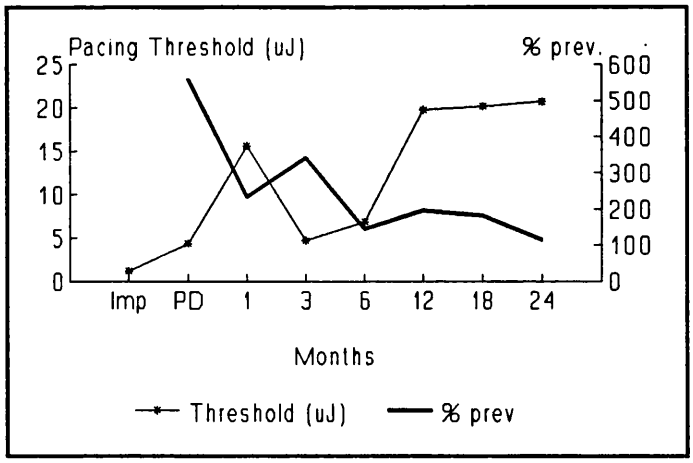

Figure 5.6: Mean chronic pacing threshold and percentage change in threshold between each visit for 13 patients with epicardial sensing leads

There was a significant rise in pacing threshold between device implant and the pre-discharge check although differences in measurement technique may again account for some of this change. The analysis suggests that there is a trend to steadily rising pacing thresholds throughout the study, albeit it at a gradually slowing rate, replicating previous observations about epicardial pacing leads (Oldershaw *et al.* 1982).

Endocardial Systems -

The pacing and sensing performance of endocardial lead systems gave rise to considerable problems in the early stages of this study. We noted that both the Endotak™ and EnGuard™ lead systems were prone to suffer a marked reduction in R-wave amplitude following defibrillation shock delivery. This problem was most common with the EnGuard™ system (Figure 5.7) but also occurred with the Endotak™ lead and resulted in the abandonment of one implant attempt with this lead when the R-wave fell from 6 to 3 millivolts after delivery of the first defibrillation shock and failed to recover. Despite repositioning of the electrode a satisfactory signal could not be obtained.

The Medtronic Transvene™ lead appears free of this problem, possibly because unlike the other two leads sensing occurs between dedicated pace-sense electrodes rather than between the tip electrode and the distal defibrillation coil.

The chronic performance of all three endocardial lead systems is shown in Figures 5.8 and 5.9.

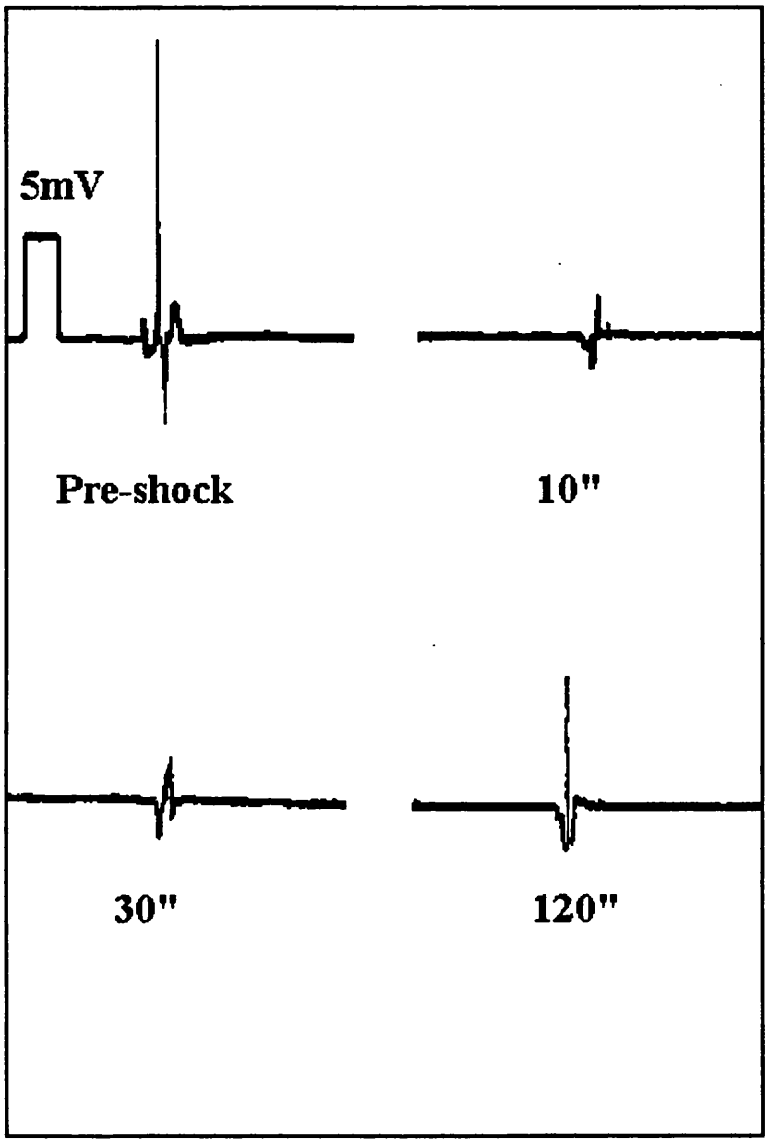

Figure 5.7: Recording of endocardial R-wave from EnGuard™ defibrillation electrode before and 10, 30 and 120 seconds after delivery of a 20 joule defibrillation shock

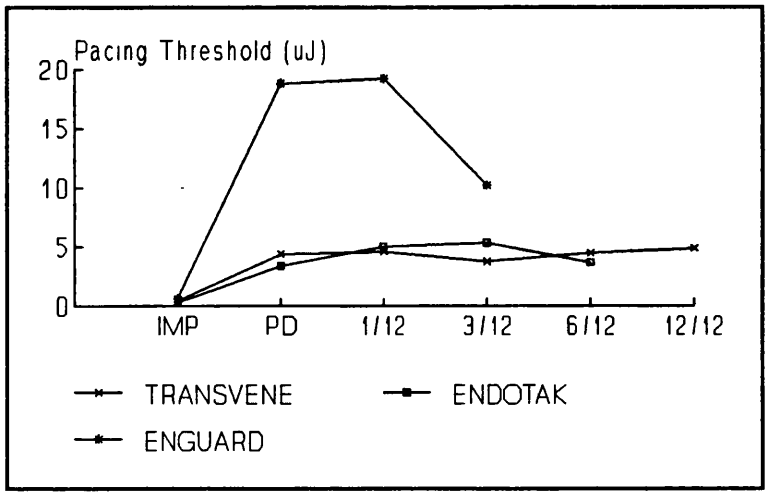

Figure 5.8: Absolute values of the pacing threshold (in microjoules) at implant (IMP), pre-discharge (PD) and subsequent follow-up for Medtronic Transvene™, CPI Endotak™ and Telectronics EnGuard™ lead systems

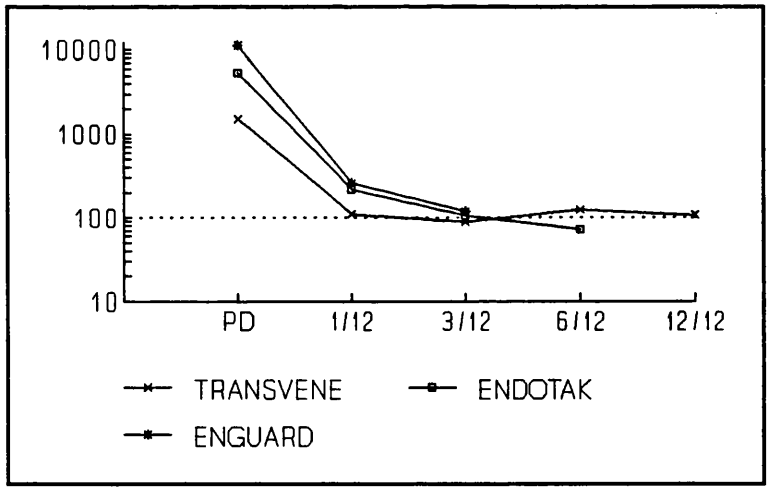

Figure 5.9: Pacing thresholds for Medtronic Transvene™, CPI Endotak™ and Telectronics EnGuard™ lead systems expressed as a percentage of those at the previous visit

Performance of the Transvene™ and Endotak™ leads appears similar with a significant ($P<0.0001$) early rise in threshold followed by long-term stability. However the rise in pacing

energy required with the EnGuard™ lead is much higher. Indeed one patient with this lead developed exit block and all patients showed a sharp rise in threshold. This observation of an early threshold rise has been observed in other centres and this lead has now been withdrawn.

With the exception of the EnGuard™ lead the performance of the pacing and sensing via the endocardial defibrillation lead compares favourably with the epicardial leads. The numbers of patients and duration of follow-up in this study are too small to allow definitive conclusions but it appears that both epicardial and endocardial leads deliver stable sensing signals in the long-term. Epicardial pacing thresholds may have a chronic tendency to rise gradually whereas endocardial pacing thresholds show no sign of this behaviour.

Post-implant sensing problems during this study have been few. One patient with a Telectronics 4202 defibrillator which has fixed gain sensing circuitry has demonstrated occasional double and even triple sensing of the R-wave (Figure 5.10). A potentially more troublesome problem has occurred with devices with automatic gain control. Double sensing of paced beats has occurred due usually to the high amplitude of the paced T-wave (Figure 5.11). This problem has occurred with all of the third-generation devices described in this thesis. Reprogramming of basal sensitivity or sometimes pacing output usually alleviates it and no clinical sequela has resulted from this problem. However, it raises doubts about the current trend towards the use of devices where there is no programmability of sensitivity whatsoever. Potentially such oversensing could interfere with the delivery of antitachycardia pacing therapies.

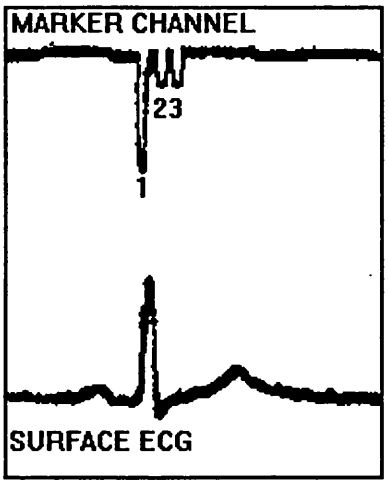

Figure 5.10: Triple R-wave sensing with the Guardian 4202 defibrillator shortly after a defibrillation shock. The marker channel shows an initial sensed event (labelled 1) coinciding with the onset of the QRS complex. This is followed rapidly by two further sensed events (labelled 2&3) which fall within the noise detection interval and are given a short marker spike. Such multiple sensing may be due to fragmentation of the sensed electrocardiogram following the defibrillation shock

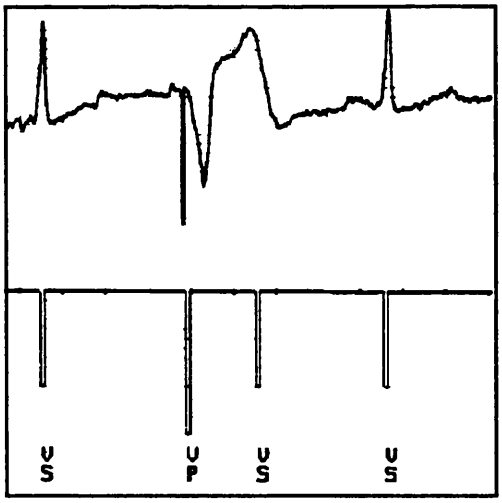

Figure 5.11: T-wave sensing following a paced beat with the Medtronic 7217 PCD defibrillator. A paced ventricular beat (VP) is followed by a sensing marker (VS) during the T wave

Defibrillation:

The limitations imposed by the study design on the assessment of long-term defibrillation performance have been discussed above. Sufficient data for analysis exist for implant, pre-discharge, 1/3-month and 12 month checks. Device performance at defibrillation checks has been classified as follows:

Safety Margin Met - Successful defibrillation has been achieved on one or more occasions using a shock of 20 joules or less

Safety Margin Not Met - A 20 joule shock has failed to defibrillate but successful defibrillation has been achieved with a shock of 34 joules or at an intermediate energy level

Safety Margin Status Unclear - Successful defibrillation has been achieved with a shock of 34 joules but lower energies have not been used most commonly because of difficulty with inducing ventricular fibrillation

On the basis of the category at each visit and that at the previous visit defibrillation status was classified as:

Improved - Safety margin met where it had not been met at the last visit

Worse - Safety margin not met where it had been met at the last visit

No change - Status unchanged or patient safety margin unclear at this visit

Patient status at each visit is shown in Tables 5.1 and 5.2.

Table 5.1: Proportion of patients with transvenous defibrillation systems meeting defibrillation safety margin at implant and at subsequent follow-up (Chi-squared = NS)

	IMPLANT		PRE-DISCHARGE		1 / 3 MONTH		12 MONTH	
	n	%	n	%	n	%	n	%
Safety Margin Met	27	82	22	67	22	73	7	100
Safety Margin Not Met	6	18	3	9	6	20	0	0
Safety Margin Status Unclear			8	24	2	7	0	0

Table 5.2: Transvenous lead system defibrillation performance at each visit compared with previous visit (p=NS)

	PRE-DISCHARGE		1 / 3 MONTH		12 MONTH	
Safety Margin Status	n	%	n	%	n	%
Improved	0	0	5	17	1	14
No change	31	94	20	66	6	86
Worse	2	6	5	17	0	0

There is no evidence from these data of any deterioration in the performance of transvenous defibrillation leads over the first 12 months after implantation. Clearly confirmation of this observation will require the study of a larger number of patients over a longer time period. One patient in the transvenous lead group who had satisfied the implant safety margin at device implant with a lead only system failed to defibrillate with a 34 joule shock at pre-discharge testing. No explanation for this was found, there being no lead displacement or change in drug therapy and the observation being confirmed by repeat testing. The system was revised with the addition of a subcutaneous patch electrode since when it has functioned satisfactorily. One epicardial system patient with poor underlying left ventricular function required three 34 joule shocks from his defibrillator to achieve defibrillation at pre-discharge testing. This patient had failed to meet the defibrillation safety margin at ICD implant although defibrillation at 34 joules had been repeatedly successful. Addition of an ACE inhibitor and more aggressive therapy for his heart failure resulted in improved ICD performance and long-term follow-up has been uneventful. He has received over 20 successful antitachycardia pacing therapies from his epicardial ICD system but has yet to require a shock therapy.

Complications of ICD use:

Epicardial systems:

Fourteen patients received epicardial ICD systems as their first implant. The in-hospital complications in this group are summarised in Table 5.3.

Table 5.3: In-hospital complications of epicardial implants.

Complication		(n)	%
Infection - Abdominal wound		2	14
	Chest	2	14
Arrhythmia -	VPC's	1	7
	Frequent VT	3	21
ICD generator pocket haematoma		1	7
Death		0	0

The commonest problem was that of exacerbation of the underlying arrhythmia, which required alteration of antiarrhythmic drug therapy in three patients. Complications occurring after hospital discharge are summarised in Table 5.4. Late infection occurred in one patient resulting in system removal. Following replacement of the system infection occurred again and during a subsequent hospital admission the patient died as a result of increasingly incessant ventricular arrhythmias after the system (excluding the epicardial patches) had been removed. Two other patients required readmission for alteration of drug therapy to control frequent episodes of ventricular tachycardia. The second death in this population occurred in a patient with scleroderma who developed progressive cardiac failure and increasingly frequent episodes of ventricular fibrillation all of which were rapidly terminated by the ICD. The patient died whilst undergoing cardiac transplantation.

Table 5.4: Out-of-hospital complications of epicardial implants.

Complication		(n)	%
Infection -	Requiring system removal	1	7
Arrhythmia -	Frequent VT requiring altered drug therapy	3	21
Erosion of ICD generator		1	7
Insulation failure requiring lead revision		1	7
Premature ICD generator failure		1	7
Death		2	14

The overall survival of epicardial defibrillation systems in this study is shown in figure 5.12. Overall survival is defined as system survival free of ICD generator replacement or complete ICD lead system replacement.

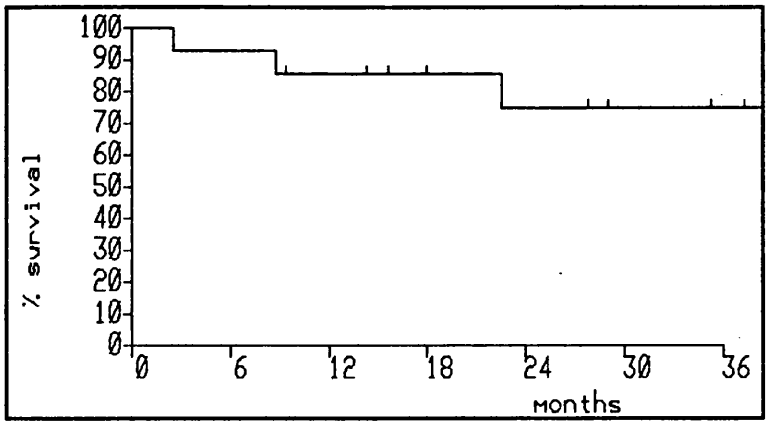

Figure 5.12: Overall survival of epicardial ICD systems

Revision free survival (defined as system survival free of component replacement or revision) is shown in Figure 5.13.

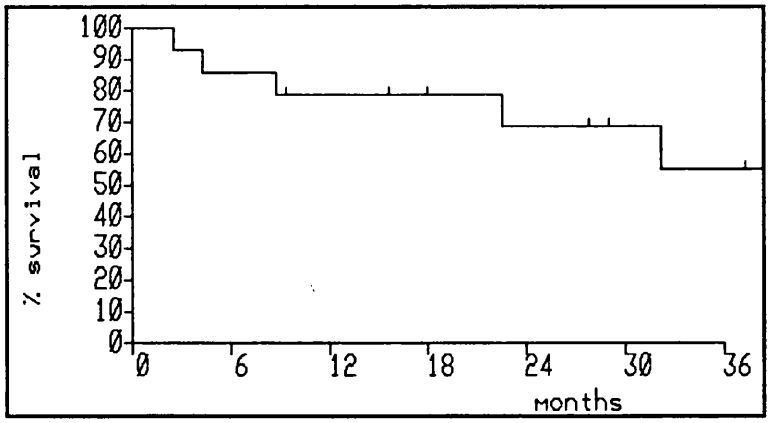

Figure 5.13: Revision-free survival of epicardial ICD systems

Transvenous Systems:

Thirty-three patients received a transvenous defibrillation system as their first ICD implant. The in hospital complications in these patients are shown in Table 5.5. Much the most common problem was the occurrence of a haematoma in either the abdominal pocket

Table 5.5: In-hospital complications with the transvenous electrode system (n=33)

Complication		n	%
Haematoma -	Axillary patch (n=29)	4	14
	Abdominal pocket	4	12
Lead displacement -	Right atrial EnGuard™	1	3
	Right ventricular Endotak	1	3
SVC lead placed in internal mammary vein		1	3
Axillary vein thrombosis		1	3
Pulmonary embolus		1	3
Urinary retention		2	6

or the axillary patch pocket. There was no significant difference in aspirin usage in these patients from the remainder. One patient with an abdominal pocket haematoma required a blood transfusion and one patient with an axillary haematoma required drainage. Two patients had thrombotic complications, one with an axillary vein thrombosis and the other with a pulmonary embolus. This patient had been taking Warfarin because of poor underlying left ventricular function and the warfarin had been discontinued to allow ICD implantation.

Complications occurring after hospital discharge are shown in Table 5.6. Lead displacements and lead fractures were much the biggest source of post-discharge problems. Lead fractures were confined entirely to the DF™ and EnGuard™ leads, both manufactured

Table 5.6: Out of hospital complications with transvenous ICD systems

Complication		n	%
Lead displacement -	DF™ - right ventricle	1	3
(reoperations)	Endotak™	1	3
	Transvene™ - right ventricle	3*	9
	- SVC	3*	9
Lead Fracture -	DF™	2	6
	Enguard™	2	6
Infection -	at site of subclavian wound	2	6
	of axillary patch	1	3
Axillary patch discomfort		8	24
Death		2	6

* - Two patients had displacement of the Transvene™ right ventricular and SVC lead together

by Telectronics. Two of three DF™ leads and two of four EnGuard™ leads suffered fractures. These leads used a nonstandard conductor material in a woven braided form, which appears to be prone to fracture under conditions of pressure and flexion. This design has now been withdrawn. All lead displacements occurred in the first six months following implant. They occurred in spite of stringent attention to lead fixing at the shoulder and, in the case of the Endotak™ lead, incorporation of a "strain relief loop".

Axillary patch related discomfort was the commonest single problem. We have analysed the occurrence of this complaint with conventional patches placed subcutaneously, conventional patches placed submuscularly and the CPI array electrode (Table 5.7). There was no statistically significant difference between the three approaches. As the submuscular patch is technically more difficult than the subcutaneous patch and failed to show any reduction in the incidence of discomfort we have abandoned this approach. The results with the array electrode are encouraging but deployment of the array is difficult and is currently available for use with the CPI Endotak™ system only.

Table 5.7: Incidence of discomfort related to axillary electrode placement.

Lead type	Proportion of patients with patch discomfort	%
Conventional patch - subcutaneous	4/17	23
Conventional patch - submuscular	4/6	67
Axillary array	0/6	0

P = NS for all comparisons

Of the two deaths in the transvenous electrode group one was due to a flare-up of ventricular arrhythmias associated with poor underlying left ventricular function. The patient

died in hospital of incessant ventricular arrhythmias which could not be terminated by shock therapies from the device or by external cardioversion/defibrillation. The second death occurred as a result of generalised sepsis and progressive impairment of myocardial function in a patient who received a Telectronics DF™ lead. A few weeks after implant the patient presented with for a routine check and was found to have a high impedance on the pacing electrode consistent with a lead break. The system was replaced with an epicardial patch system and the patient had a long, complicated post-operative course culminating in his death five weeks later.

The overall survival of endocardial defibrillation systems in this study is shown in Figure 5.14.

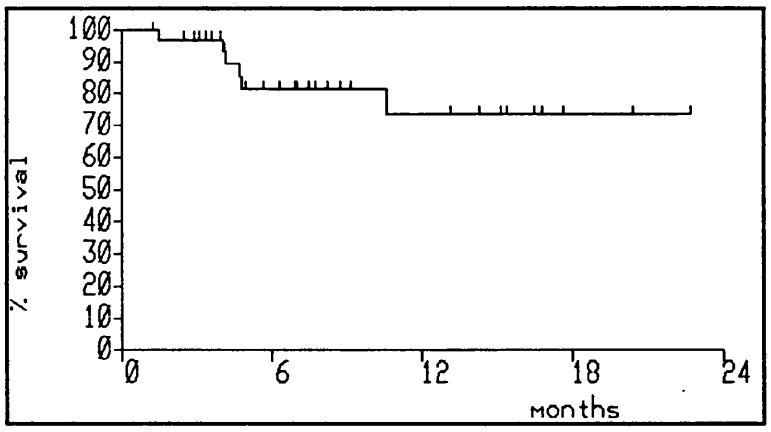

Figure 5.14: Overall survival of endocardial defibrillation systems in this study

Cumulative survival falls to 80% by six months and 74% by 12 months remaining stable thereafter reflecting the early occurrence of the lead fractures and infections which were the common cause for system failure. The survival of the systems without revision is shown in Figure 5.15.

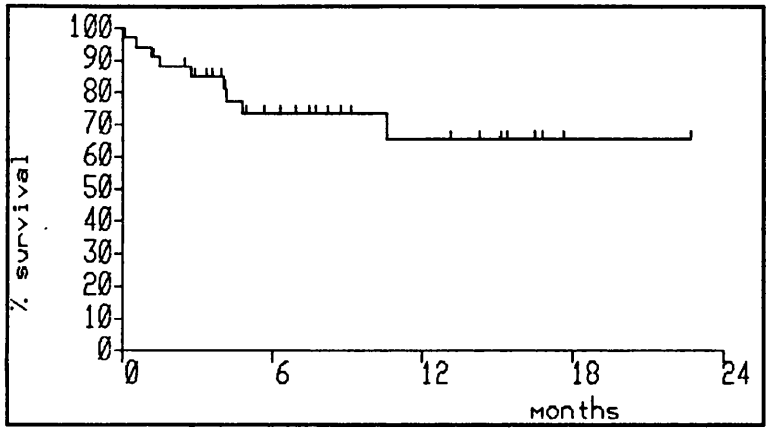

Figure 5.15: Revision-free survival of endocardial defibrillation systems

Because of the high incidence of problems noted with the Telectronics leads we have analysed survival for Telectronics versus the other manufacturers lead system separately (Figure 5.16). The difference is dramatic and highly significant statistically ($p<0.0001$).

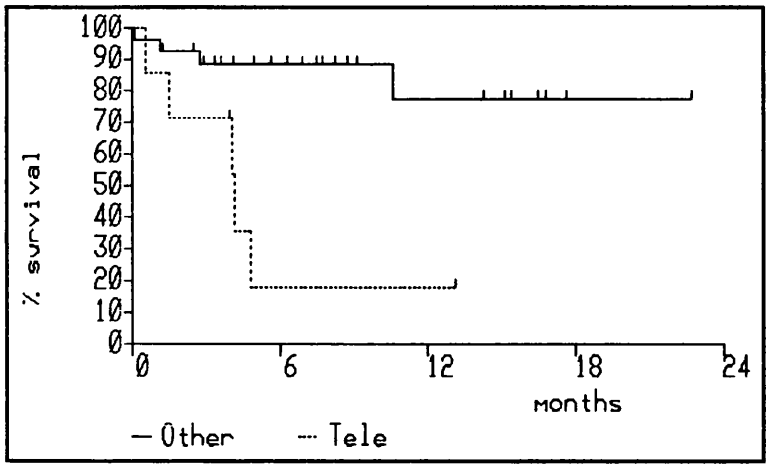

Figure 5.16: Revision-free survival of Telectronics systems (Tele) versus other manufacturers (Other)

Discussion:

Whilst the primary outcome by which the success of ICD therapy may be measured is the prevention of sudden cardiac death the stability of the long-term performance of the device and a low incidence of adverse effects are important if the therapy is to be acceptable to patients and physicians. Endocardial defibrillation systems are in their infancy and it is important to assess whether they at least match and preferably better the performance of existing epicardial lead systems particularly as doubts about their performance have been expressed (Saksena 1992).

The conclusions which can be drawn from this study are limited because of the relatively small number of patients and the limited duration of follow-up. Nonetheless a number of important issues have been highlighted by this study.

There is considerable scope for improvement in the pacing and sensing performance of both epicardial and endocardial lead systems. One patient had inadequate sensing with epicardial leads at the time of ICD implant despite the use of multiple electrode sites. This is likely to be even more of a problem with the more limited thoracotomies now used or with system implant via thoracoscopy suggesting that in centres where epicardial patches continue to be used endocardial pacing and sensing may become standard. Although post-implant sensing remained satisfactory there was a suspicion of a steady rise in pacing threshold throughout the life of the epicardial pacing leads, possibly replicating that already noted with conventional epicardial pacing leads (Oldershaw *et al.* 1982). However the simplicity and conventional construction of epicardial electrodes was reflected in the lack of lead failure problems in this group of patients.

A number of pacing and sensing problems were noted with endocardial leads. Two implants (one Endotak™ and one Transvene™) were abandoned due to difficulty in obtaining satisfactory pacing thresholds and R-wave amplitudes. Multiple repositioning within

the ventricle was often required to obtain satisfactory values and with the Endotak™ and EnGuard™ lead marked loss of R-wave amplitude in the immediate post-shock period was frequently noted, resulting in abandonment of an implant in another patient. Despite the difficulties with lead positioning the mean implant time for transvenous systems was 160 minutes compared with 176 minutes for epicardial systems. Long-term pacing and sensing values were stable and satisfactory with the Endotak™ and Transvene™ lead systems but it became clear during the study that the DF™ and EnGuard™ lead systems were prone to early post implant rises in pacing thresholds to levels at or above the maximum output of the ICD. Subsequent work by the manufacturers has suggested that this may be due to leakage of up to 10% of defibrillating current through the pacing electrode at the tip of the lead, resulting in high current densities and tissue damage.

Long-term testing of defibrillation efficacy was limited to transvenous electrode systems only. Over the first twelve months follow-up there was no evidence of any deterioration in defibrillation efficacy with over 75% of patients undergoing defibrillation testing at energies of 20 joules or less meeting the safety margin criteria. Substantial crinkling of patch electrodes was noted on routine chest radiograph in two patients with epicardial systems. Defibrillation efficacy testing was performed in these patients and both achieved reliable defibrillation with 20 joules. All out-of-hospital episodes of ventricular fibrillation were successfully terminated by the ICD over the study period.

The incidence of in-hospital complications showed some significant differences between the epicardial and transvenous implants. The incidence of arrhythmia exacerbation following surgery was significantly higher (21%) than in the transvenous group (0%) $p < 0.05$. Because of the additional potential for haematoma collection in the axillary patch pocket haematomas appeared more common in the transvenous group and transvenous leads clearly have the potential to act as a focus for thrombosis. We have not assessed the post-operative formation of thrombus on the transvenous electrodes but it has been reported in 16% of patients (Jung

et al. 1993) and some centres routinely anticoagulate their patients (Block *et al.* 1992) with transvenous leads. In view of the incidence of haematoma formation the risks and benefits of such an approach deserve careful consideration.

The generally more rapid recovery following ICD implant in the transvenous electrode group is reflected by the significantly ($p<0.05$) shorter hospital stay (mean 8.1 days) compared with the epicardial group (13.6 days).

The primary source of late complications in the transvenous system group was problems with the electrode systems. Endocardial lead displacement was noted in 6 patients (18%) and affected all three transvenous lead systems (and in the two lead systems both leads). Where system performance was unaffected no action was taken but 3 patients required revision of their lead system because of this. The two Telectronics leads used in this study showed a very high incidence of conductor fracture and this again appeared to be related to the design of these electrodes. In four patients where lead fracture occurred major system revision or complete replacement was required and in one case this may have been responsible for patient death. Axillary patch related discomfort was a problem in 25% of patients with transvenous lead system but no system required revision because of this. It is important to remember that the transvenous lead systems used in this study represent new and experimental technology. The leads are subject to mechanical and electrical stresses far in excess of those to which conventional transvenous pacing leads are exposed. Their long subcutaneous course in the chest renders them vulnerable to external damage and may explain the high incidence of displacement noted in this study. The rapidity with which problems with the leads have been recognised and lead design modified suggests that improvements in performance will be rapid.

The incidence of late infection did not differ significantly between epicardial (7%) and transvenous (9%) systems. In all cases infection eventually required system replacement or

removal and replacement of the infected component, therapy with antibiotics proving ineffective. The infections appeared indolent and no organism was cultured. In addition to prophylactic antibiotics we now use pre-operative Chlorhexidene baths and aqueous Betadine is used in wounds which require revision but it is not yet clear whether this will reduce the risk of infection.

Comparing the revision free survival of epicardial and transvenous defibrillation systems there is no significant difference between them whether the Telectronics systems are included (Figure 5.17) or excluded (Figure 5.18).

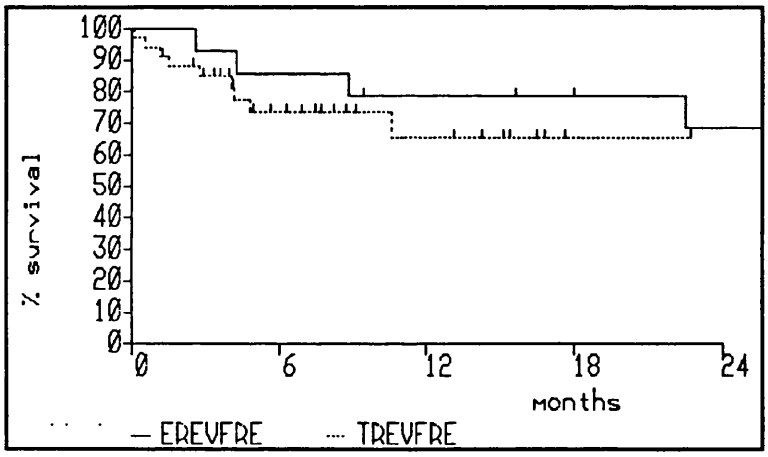

Figure 5.17: Revision-free survival of epicardial (EREVFRE) versus all transvenous (TREVFRE) systems. Although overall transvenous survival appears worse this is not significant by the Logrank test

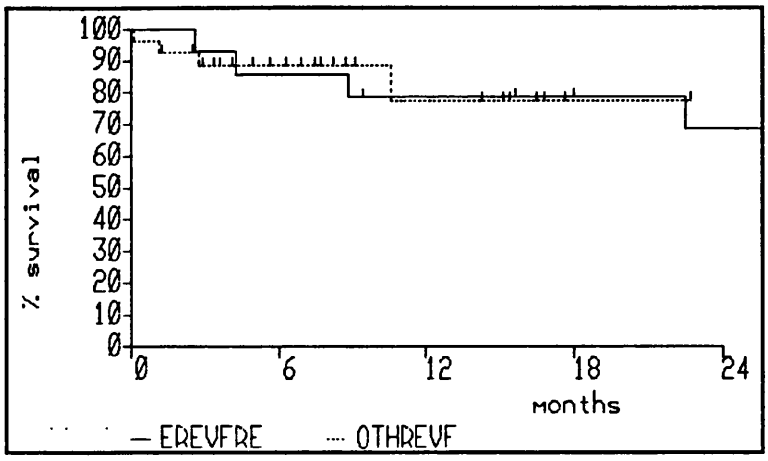

Figure 5.18: Revision-free survival of epicardial (EREVFRE) versus Medtronic and CPI transvenous defibrillation system (OTHREVF). Revision free-survival is very similar in the two groups

Conclusions:

It is clear from this study that transvenous defibrillation electrode systems are still at a relatively early stage of development and that some designs have been found wanting when exposed to the many demands which must be satisfied by such a lead system. Whilst this study is too small to confirm the observations of other studies that transvenous lead systems are associated with a lower implant mortality we can draw some conclusions about the long-term performance of these systems. Obtaining satisfactory pacing and sensing at lead implant may be difficult and may require several lead positions to be tried. However once a satisfactory position has been obtained the long-term performance of the leads is generally good and may be superior to that of epicardial lead systems. Transvenous defibrillation leads are exposed to high physical stresses due to their length and this is reflected in the relatively high incidence of lead displacement and (with certain lead systems only) lead fracture. Such problems frequently require revision of the system. This study suggests that the defibrillation

performance of such lead systems is stable, at least over the first 12 months after implantation and the continued clinical effectiveness of these systems, even when defibrillation safety margins are narrow, is encouraging. There is a significantly lower incidence of post-operative arrhythmias in the patients with transvenous electrodes but no clear difference in other post-operative complications. Ignoring the problems with lead fracture and displacement the problems are largely what might be expected from the nature of the implanted hardware. System infection remains the most serious complication whilst axillary patch related discomfort is the most common. Hopefully with the increasing availability of lead-only implants this will become less of a problem.

In our small series it is not clear that transvenous lead systems have realised their potential for reduced mortality and morbidity although they are clearly associated with a shorter hospital stay. It is important to remember that this experience encompasses the learning curve of several operators and the early evaluation by manufacturers of lead systems, not all of which have survived unscathed. This small study suggests that when technical and design problems have been resolved transvenous defibrillation systems will meet and probably exceed the performance of current epicardial systems, particularly if the increasing use of biphasic shock waveforms enables the axillary patch electrode to be dispensed with.

** ** ** ** **

CHAPTER 6:

THE IMPACT OF ARRHYTHMIAS ON PSYCHOMOTOR PERFORMANCE. AN ANALYSIS OF THE RISKS ASSOCIATED WITH DRIVING A MOTOR VEHICLE IN PATIENTS WITH AN IMPLANTABLE DEFIBRILLATOR:

Introduction:

During the course of this study it became clear that the biggest disadvantage of ICD therapy for most patients was the current ban on driving in the United Kingdom for patients with the device (Gold & Oliver 1990). In some patients this has restricted their continued employment and all patients have found it a major inconvenience. Whilst these regulations have been created with the safety of the general public in mind they date from a time when little was known about the long-term outcome of patients treated with the ICD and are overdue for review. These regulations contrast dramatically with those in the United States where few states have any specific regulations concerning driving with arrhythmias or the ICD (Strickberger *et al.* 1991). The major concern about allowing ICD patients to drive is the risk of syncope due to the occurrence of haemodynamically unstable arrhythmias. Implicit in the use of the ICD is the recognition that the patient may suffer from such episodes. Additionally it has become clear that even patients whose ventricular arrhythmias have previously been haemodynamically stable may suffer future haemodynamically unstable episodes (Kou *et al.* 1991) or syncopal episodes as a result of the acceleration of stable arrhythmias by attempted antitachycardia pacing (Holley *et al.* 1986). It is for this reason that the ICD has largely supplanted the use of simple antitachycardia pacemakers for ventricular tachycardia. An additional concern relates to the impact of haemodynamically stable arrhythmias and whether these may cause impairment of concentration, even when successfully terminated by

antitachycardia pacing. Although the factors which cause syncope during ventricular tachycardia have been studied in detail (Hamer *et al.* 1984) and the impact of ventricular tachycardia on carotid artery blood flow has been recorded (Benchimol *et al.* 1974) the impact of presyncopal arrhythmias on psychomotor function has not been studied.

This study is therefore in two parts. In the first part a study to assess the psychomotor and haemodynamic effects of nonsyncopal symptomatic and asymptomatic arrhythmias is performed. The second part consists of an analysis of the risk of allowing ICD patients to drive, in comparison with other groups of patients known to be at risk of syncope.

PART I: THE EFFECTS ON PSYCHOMOTOR PERFORMANCE OF SYMPTOMATIC AND ASYMPTOMATIC VENTRICULAR ARRHYTHMIAS.

Methods:

Because of our particular interest in the impact of arrhythmias on driving performance we wished to use a psychomotor task which demanded analogous skills. Unfortunately, most psychomotor tests have been developed to assess the impact of pharmaceutical agents on performance and because the actions of a drug usually last for hours the tests have been optimised to score steady-state performance. Although full-scale driving simulators have been used to measure steady-state psychomotor performance (Willumeit *et al.* 1984) a visit to the Transport and Road Research Laboratory suggested that scoring of short term changes in performance using such a complex task was impractical, in addition to the risks of inducing arrhythmias in such an environment! Accordingly it was necessary to develop our own psychomotor task which could be scored over short periods of time. With the aid of the Department of Psychology a computer program was written in Quick Basic which performed a modified pursuit rotor task. A small circular target tracks at a constant speed around a

circular course on the computer screen (Figure 6.1). Using a minimal inertia unsprung joystick (Royal Aircraft Establishment, Farnborough) the patient is asked to track the course of the target using a cross hair. Performance is scored three times per second on the distance between the target and the cross hair and this score is stored with a timing signal on the computer. The patient performs the task sitting upright in a comfortable chair facing the computer screen.

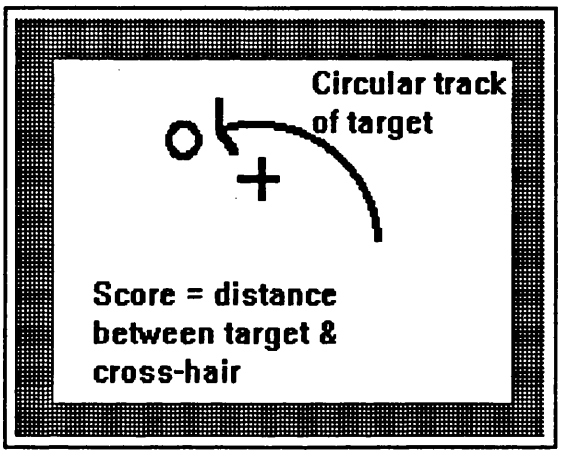

Figure 6.1: The psychomotor tracking task using a small round target travelling a regular circular course. The patient tried to maintain the cross-hair in the centre of the circle at all times

To enable the blood pressure to be measured and stored simultaneously an Ohmeda Finapres 2300 finger cuff system was used. This measures blood pressure by a pneumatic cuff on the finger and has been shown to give an excellent correlation to arterial blood pressure (Parati *et al.* 1989, Friedman *et al.* 1990). The analogue output from the Finapres was fed into an analogue-digital converter and recorded by the computer simultaneously with the psychomotor scores enabling accurate correlation of blood pressure and psychomotor performance. The difference in height between the finger cuff and the angle of the jaw was

measured and fed into the computer to approximately compensate the blood pressure values to that reaching the cerebral circulation.

This psychomotor test was evaluated in 15 patients undergoing investigation for ventricular arrhythmias or awaiting coronary artery bypass grafting. We found that patients could tolerate continued performance of the tracking task for at least three periods of five minutes with a five minute rest in between, without visible evidence of a deterioration in performance, severe boredom or fatigue, provided that the level of difficulty (speed of rotation of the target) was adjusted so that they were able to maintain a mean deviation score of 75 (arbitrary) units or less. Figure 6.2 shows the recording from a standard five minute test period.

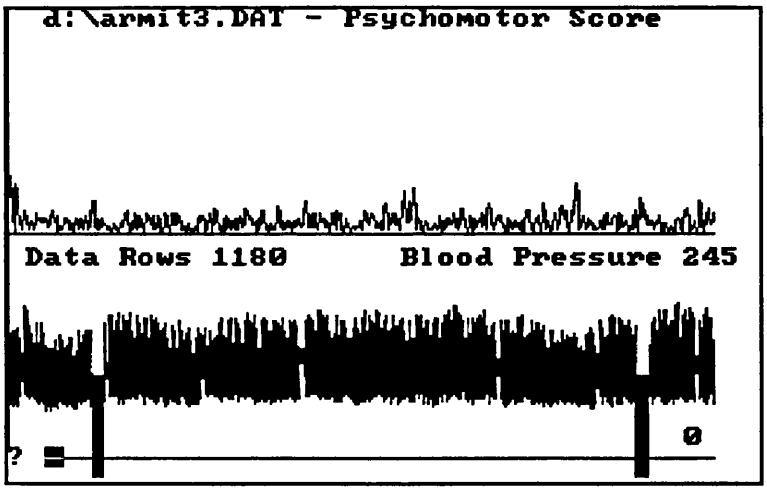

Figure 6.2: Psychomotor score (top trace) and blood pressure (bottom trace) recorded for five minutes in a control study

The psychomotor score is shown along the top of the plot and it can be seen that there is inevitably some baseline variation in score but that overall performance is well maintained

over the five minute period. Blood pressure is shown in the bottom half of the tracing. The blood pressure recording is interrupted at the beginning and end by a calibration signal sent from the Finapres which enables correction for any drift between the Finapres and the computer. Most patients showed a small but significant rise in blood pressure of 3-4mm Hg during each five minute period. This change resolved rapidly when the psychomotor task was completed.

Carotid flow measurement:

Doppler ultrasound of the carotid artery was used to assess cerebral blood flow as the equipment was already available and the technique had previously been validated by others (Leopold *et al.* 1987). An Acuson L7384 7.5MHz ultrasound probe was used to visualise a segment of the internal carotid artery and the flow velocity measured by pulse Doppler. A validation study was conducted using a phantom neck produced by the Department of Physics. This contained tubes of 4mm and 6mm diameter at an angle of 30° to the surface. A starch solution flowed through these tubes from a reservoir whose height could be varied to alter the flow velocity. Absolute flow velocity in a given tube was calculated by collecting the flow from the tube for a period of one minute. Flow velocity derived from the ultrasound probe, corrected for the incident angle of the ultrasound, was multiplied by the cross sectional area of the plastic tube in the phantom to calculate flow. This area itself was calculated by the diameter measured from the ultrasound image. Figure 6.3 shows the excellent correlation between measured and absolute flow with a 4mm and 6mm tubes at a depth of 2cm. The Doppler ultrasound overestimated absolute flow by about 30% but this overestimate appeared constant over a two-fold range of flows. The linear nature of the relationship between measured and true flow is maintained at depths of up to 4cm as shown in figure 6.4.

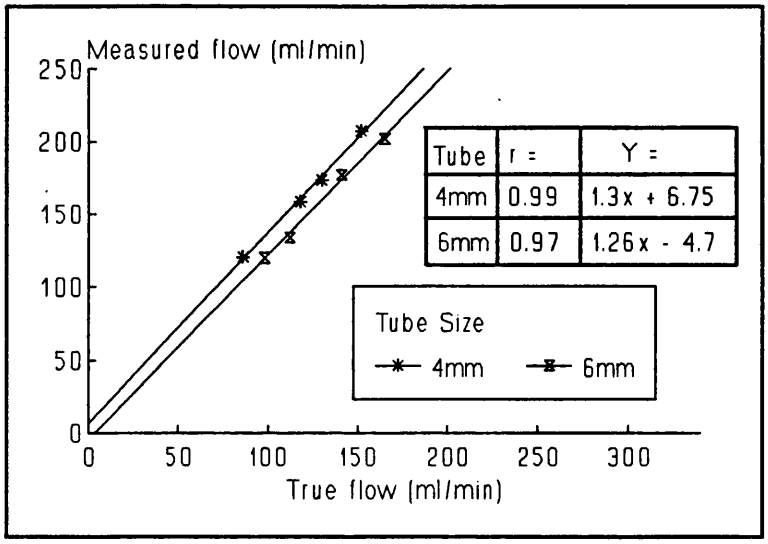

Figure 6.3: Measured flow using doppler ultrasound versus true flow in 4mm and 6mm plastic tubes at a depth of 2cm in a phantom neck model. The measured flows overestimate true flow by approximately 30% but the response is linear with a very good correlation coefficient

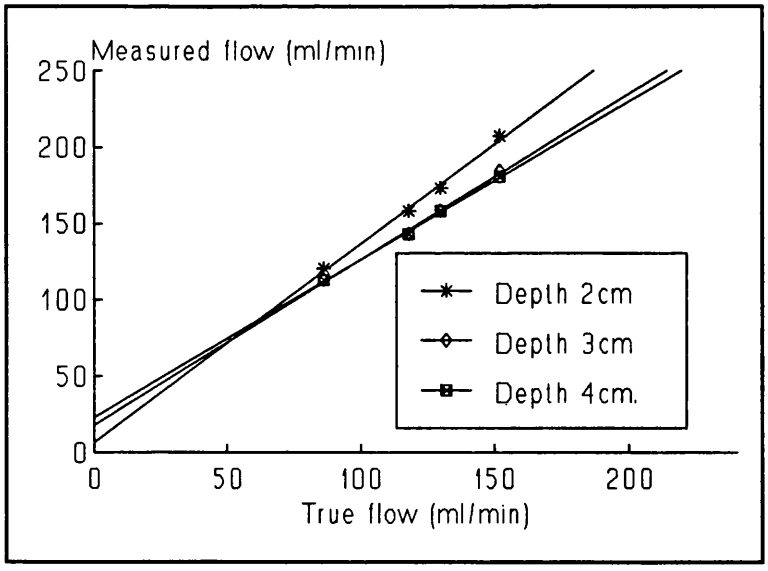

Figure 6.4: Relationship between measured and true flow in a 4mm plastic tube at depths of 2, 3, and 4cm in the phantom neck

The accuracy and reproducibility of this method of flow measurement is dependent on operator experience and deteriorates with the duration of the examination as the Doppler probe has to be held in position by hand. To verify the stability of Doppler flow measurements over a period of one minute as required by this protocol a simple study was performed in 50 normal carotid arteries identified in patients referred for carotid artery ultrasound. Doppler flow velocity measurements were made continuously for a period of one minute with the patients sitting in a chair at rest in a quiet, darkened room. Flow velocities during the first and last five seconds of the minute were measured and the flow velocity in the last five seconds expressed as a percentage of that during the first five seconds. The mean value was 101% with a standard deviation of 3.7%. The expected changes in carotid flow during the active part of this study were 20 - 50% over a 30 second period so this technique should be capable of resolving these changes adequately.

To ensure reproducibility of the arrhythmia it was decided to use ventricular pacing rather than spontaneous arrhythmias in this study. This had the advantage that the heart rate could be adjusted precisely to achieve the desired symptoms and the onset of the episode would not be obscured by the drive train necessary to induce clinical ventricular tachycardia.

The majority of studies of arrhythmia haemodynamics have been conducted with the patient recumbent. However most attacks of arrhythmia occur during the day when the patient is sitting or standing. For this reason and also to mimic the situation when the patient is driving we decided to conduct this study with the patient sitting-up in a standard padded office swivel chair. To minimise the risk of injury should a patient inadvertently become syncopal during the study mattresses and soft pillows were placed around the chair. Full resuscitation facilities were available in the room. A standard experimental protocol was adopted for this study:

PHASE 1 - 4-minute practice session for psychomotor task. The task is available in three levels of difficulty (governed by the speed of rotation of the target) and the practice session starts with two minutes at the easiest level followed by a minute at an intermediate level and a further minute at the most difficult level (Figure 6.5). The level of difficulty chosen for the formal testing sessions was the most difficult level at which the subject achieved a mean deviation score of 75 units or less.

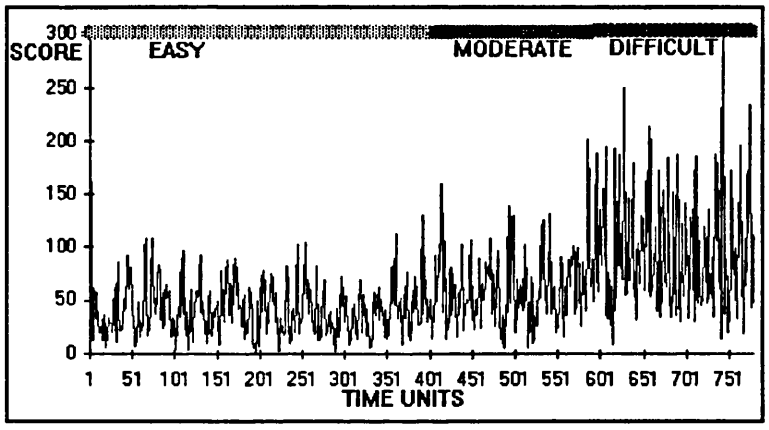

Figure 6.5: Practice psychomotor protocol over four minutes. The deterioration in performance as the test becomes more difficult is clearly seen. Each time unit is approximately 310ms

PHASE 2 - Incremental Pacing Protocol. Thirty seconds of right ventricular pacing at 500ms cycle length was followed by thirty seconds for recovery and then thirty seconds of pacing at 450ms. This pattern was continued with the pacing cycle length reducing in 50ms steps until pacing resulted in transient (less than 5 seconds) haemodynamic symptoms (light-headedness, greying of vision, etc). If symptoms persisted for more than five seconds pacing was

terminated and the cycle length of subsequent pacing bursts adjusted in 10ms steps to achieve the desired duration of symptoms. This pacing cycle length was designated **FAST**. A second pacing cycle length 80ms longer than **FAST** was designated as **SLOW**. The only symptom produced by pacing at this cycle length was palpitation. The value of 80ms was chosen arbitrarily from initial pilot studies as the rate remained sufficiently fast to achieve patient awareness of palpitations but not to cause haemodynamic symptoms.

PHASE 3 - Three five-minute psychomotor test sessions separated by five minutes rest. The format of each five-minute test session is shown in Fig. 6.6. After a one minute run-in to stabilise performance on the psychomotor test four thirty-second bursts of pacing are delivered separated by 30 seconds of sinus rhythm. Two of the pacing bursts are **FAST** and two are **SLOW** and the order of delivery is random.

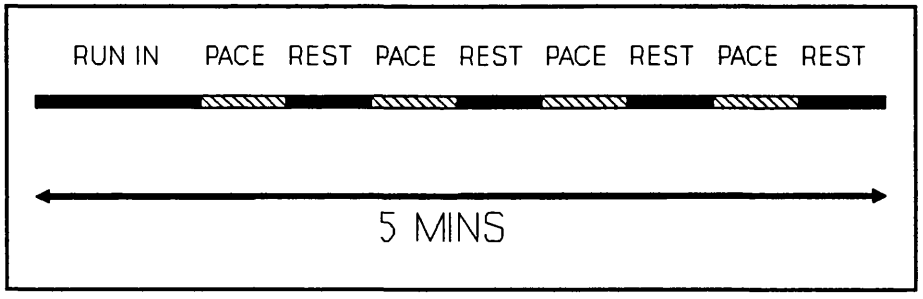

Figure 6.6: Distribution of pacing and rest periods during the five-minute study period

The simultaneous blood pressure and psychomotor score recording from a 5-minute study protocol is shown in Figure 6.7 and the acute changes in the first 15 seconds of pacing in Figure 6.8.

PHASE 4 - Unfortunately it is not possible to record carotid artery flows during the main part of the study as patient movement interferes with the reproducibility of the measurements and application of the ultrasound probe would distract the patient. Therefore, during Phase 4 internal carotid artery flow velocity is measured during 30-second pacing bursts at the **FAST** and **SLOW** rates to observe the impact of the pacing. A typical carotid flow pattern at the onset of rapid pacing is shown in Figure 6.9.

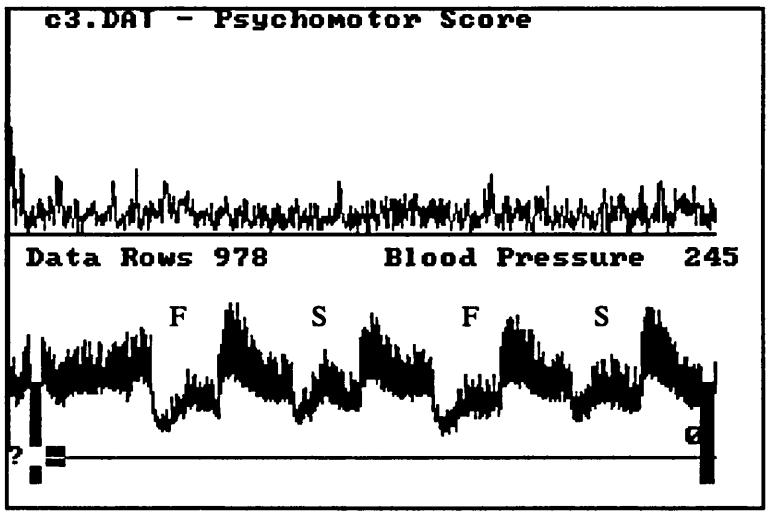

Figure 6.7: Simultaneous recording of psychomotor score (top tracing) and blood pressure (bottom tracing) during a five-minute study protocol. The periods of fast (F) and slow (S) pacing are shown. Fast pacing produces a more marked fall in blood pressure. There is no obvious impact on the psychomotor deviation score

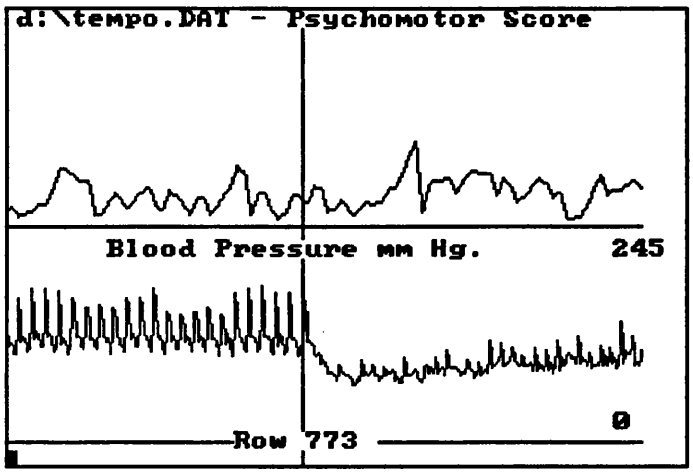

Figure 6.8: The pattern of change in blood pressure and psychomotor score over a 30-second period including the onset of rapid pacing (At line marked Row 773). A rapid drop in blood pressure with subsequent recovery is seen. A small rise in psychomotor score indicating impaired performance can also be seen

Patients:

Ten patients took part in this study. Six were undergoing investigation of spontaneous ventricular arrhythmias and had ventricular pacing wires *in situ* and the remaining four already had ICD implants which could be used to deliver the rapid pacing required. Thus no additional invasive procedure was required to perform this study. The mean age of the patients was 47 years (range 22 - 70 years) and ejection fraction ranged from 24 to 75%. All patients gave informed consent and approval for this study was obtained from the institutional ethics review board.

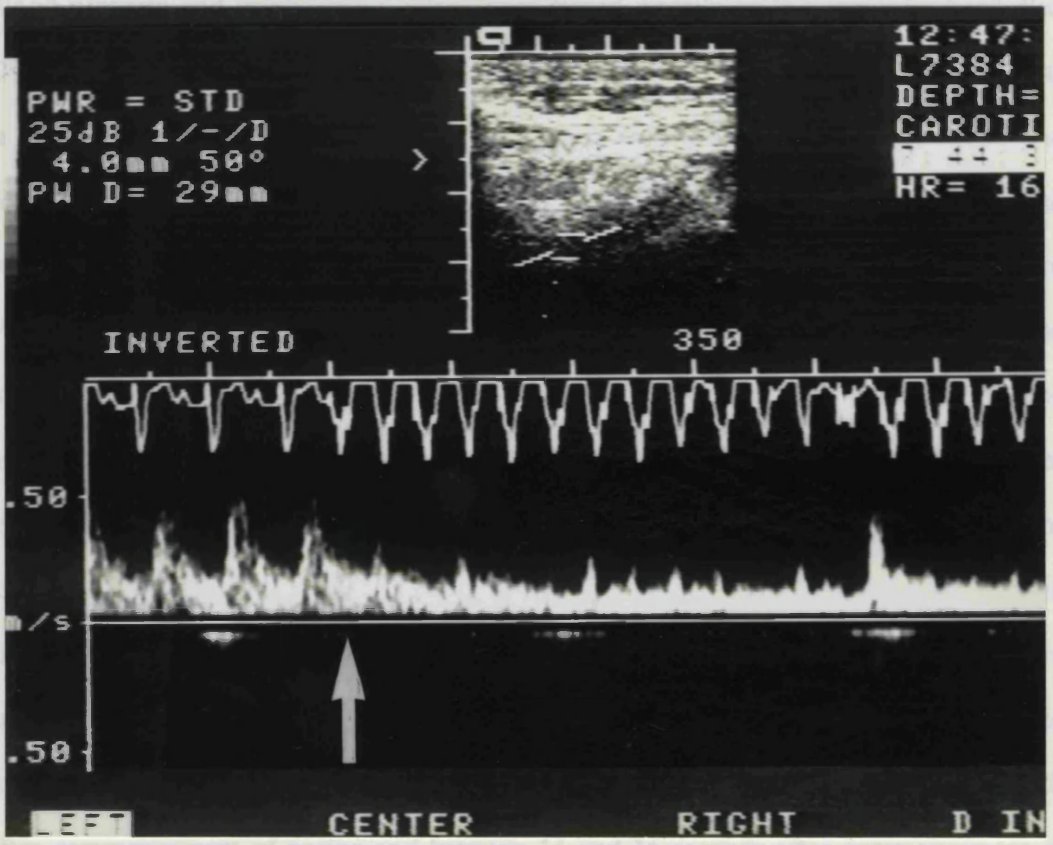

Figure 6.9: Carotid Doppler flow measurement at the onset of pacing at 350ms cycle length. The small 2-D image in the upper half of the screen allows confirmation of correct alignment with the vessel. The lower trace shows the ECG the decay of carotid artery flow velocity following onset of rapid pacing (white arrow).

Analysis:

Blood pressure and psychomotor scores were stored directly on the computer hard disc. Carotid flow measurements were recorded on videotape and mean carotid flow was calculated by measuring the area under the velocity curve. Analysis of blood pressure and psychomotor function were performed using analysis software written by the author. Because of the considerable baseline variability in psychomotor performance the psychomotor score was averaged out over a 15 second period. Baseline psychomotor function was defined as the score in the 15 seconds prior to the delivery of pacing. Mean psychomotor score during the first 15 seconds of pacing, the second 15 seconds of pacing and during the 15 seconds after termination of pacing were compared with this score and expressed as a ratio of it. The ratios for all ten subjects during **FAST** and **SLOW** pacing and during recovery were pooled and analyzed using the Wilcoxon signed rank sum test. Baseline measurement for blood pressure and carotid artery flow velocity was the mean value during a five second period prior to commencement of pacing. This was compared with the mean value between 2 and 4 seconds after commencement of pacing and between 14 and 16 seconds after commencement of pacing. Again these figures were expressed as a ratio. These timings were chosen on the basis of pilot studies which showed that the 3-4 second period coincided with the peak drop in blood pressure at the onset of pacing whilst the compensatory recovery in blood pressure was fully developed by 14-16 seconds. To ensure there was no overall trend in psychomotor performance the ratio of the psychomotor score in the 15 seconds after termination of pacing with that prior to pacing was calculated. Carotid flow and blood pressure were measured at the end of this period to assess return to baseline values. The timing of data collection for analysis is summarised in Figure 6.10.

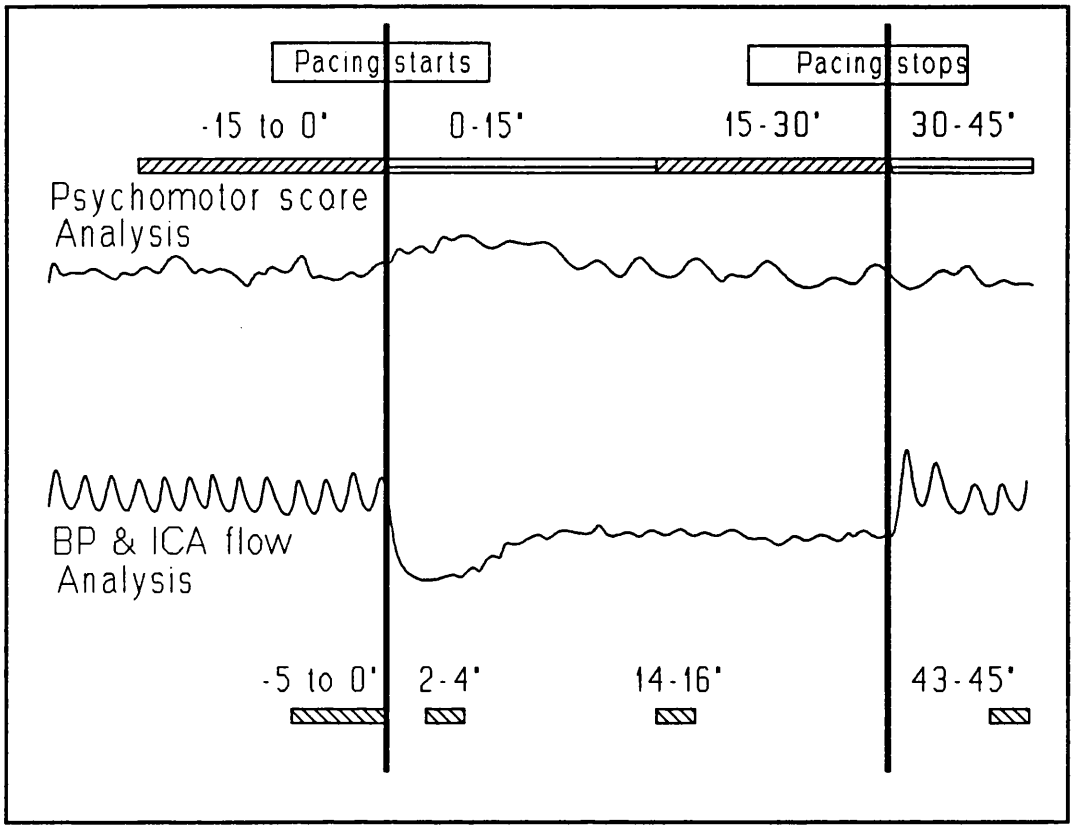

Figure 6.10: The timing of collection of psychomotor score, blood pressure and internal carotid artery flow data for analysis

Results:

Figure 6.11 shows the distribution the pacing cycle lengths used for **FAST** pacing in the ten subjects. Six of the ten subjects had inducible monomorphic ventricular tachycardia. Two of the three subjects whose tachycardia cycle length was shorter than the cycle length used for **FAST** pacing had haemodynamically unstable tachycardias. Of the three subjects whose tachycardia cycle length was longer than that used for **FAST** pacing all had haemodynamically stable tachycardias during electrophysiologic study and were not syncopal when the tachycardias occurred out-of-hospital.

The results of the pooled data for psychomotor score, blood pressure and carotid artery flow from the 10 subjects during fast and slow pacing are shown in Tables 6.1 and 6.2 and Figure 6.12. It is clear that during the **SLOW** pacing during which patients were aware only of palpitations that there was no significant impairment of psychomotor performance. Blood pressure and carotid flow fell dramatically at the onset of pacing to 64 and 66% of baseline values respectively. However by 15 seconds blood pressure had returned to 86% of baseline and carotid flow to 96% of baseline. During **FAST** pacing patients psychomotor performance fell to 79% of baseline in the first 15 seconds and continued to fall to 69% of baseline during the second 15 seconds. Blood pressure fell to 46% of baseline and carotid flow to 43% of baseline by 2 - 4 seconds after the onset of pacing. By 15 seconds blood pressure had recovered to only 67% of baseline but carotid flow had recovered to 99% of baseline. Following termination of both **FAST** and **SLOW** pacing psychomotor function returned to values close to those at baseline with a small overshoot of blood pressure and carotid flow.

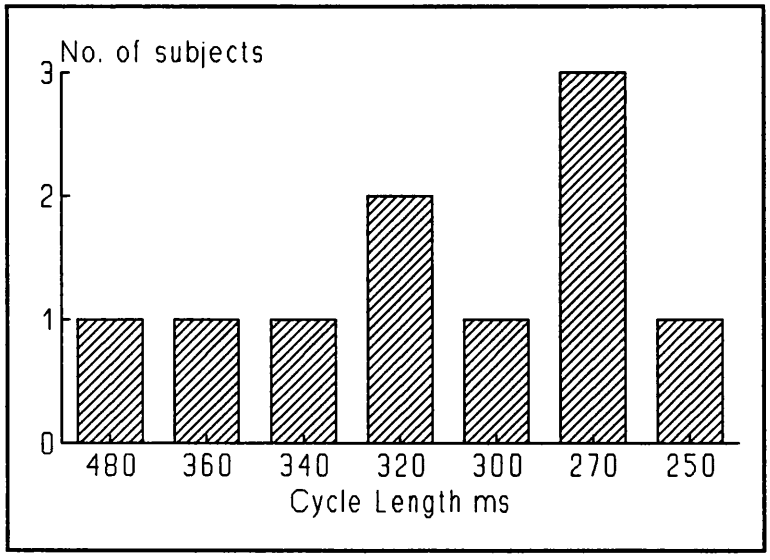

*Figure 6.11: Pacing cycle lengths used in **FAST** pacing protocol*

Table 6.1: Pooled blood pressure, carotid flow and psychomotor data during SLOW pacing

SLOW PACING	Baseline					Recovery
**** - P<0.01 NS - P = NS**		2-4	0-15	14-16	15-30	
Mean Blood Pressure % baseline (mm Hg)	100 (83)	64 (54)		86 (71)		106 (88)
Int. Carotid Flow %	100	66		96		102
Psychomotor Performance %	100		94^{NS}		96^{NS}	95

Table 6.2: Pooled blood pressure, carotid flow and psychomotor data during FAST pacing

FAST PACING	Baseline					Recovery
**** - P<0.01 NS - P = NS**		2-4	0-15	14-16	15-30	
Mean Blood Pressure % baseline (mm Hg)	100 (84)	46 (39)		67 (56)		106 (89)
Int. Carotid Flow %	100	43		99		104
Psychomotor Performance %	100		79^{**}		69^{**}	102

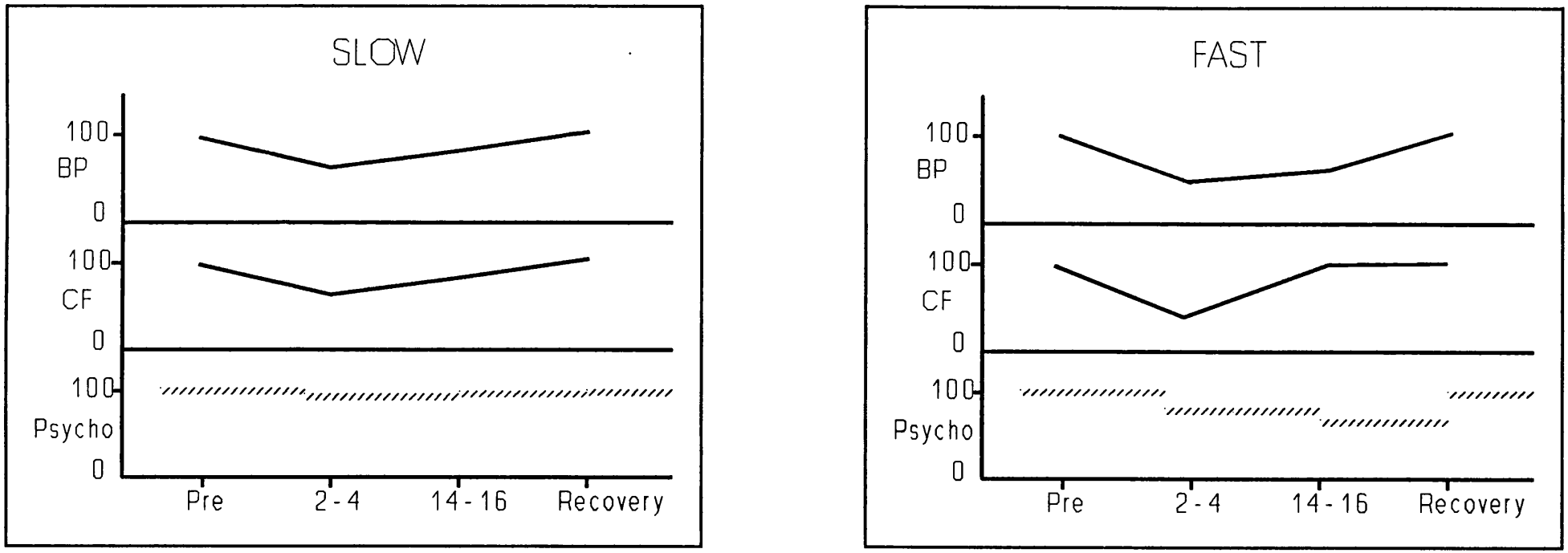

*Figure 6.12: The impact of **SLOW** and **FAST** pacing on blood pressure (BP), carotid flow (CF) and psychomotor score (Psycho) expressed as a percentage of their baseline values. **SLOW** pacing has no significant impact on psychomotor function whilst **FAST** pacing produces significant impairment, which persist after cerebral autoregulation has restored carotid flow to near baseline levels*

Discussion:

Although there have been a number of studies of the impact of cardiac surgery (Shaw *et al.* 1986) and cardiovascular drugs (Broadhurst *et al.* 1980) on chronic psychomotor function no previous study has attempted to assess the transient impact of short lived ventricular arrhythmias. The increasing use of the ICD, and in particular devices with antitachycardia pacing functions, implies that there will be an increasing number of patients who experience transient episodes of ventricular arrhythmia which may or may not cause significant haemodynamic symptoms. This study investigates the impact of such transient arrhythmias with a modified version of a conventional psychomotor test, and noninvasive measurement of blood pressure and cerebral blood flow. By using patient symptoms to define the pacing rate used it enables consideration of the impact of arrhythmias in relation to the severity of the symptoms which they cause, rather than their rate. Additionally this study has the advantage of being performed with patients sitting upright and can therefore be more reasonably extrapolated to what happens when arrhythmias occur during normal daily activities. Whilst the tracking task used to assess psychomotor performance clearly does not reproduce the varying demands of a task such as driving impairment of performance under the influence of drugs has been shown to be similar for real driving and for target tracking (Hansteen *et al.* 1976).

Episodes of arrhythmia which cause only awareness of palpitations are associated with dramatic initial haemodynamic changes but these rapidly resolve and there is no detectable impairment of psychomotor performance during these episodes. Conversely episodes of arrhythmia which are associated with symptoms of cerebral hypoperfusion such as light-headedness or greying of vision cause significant impairment of psychomotor performance. Despite rapid resolution of the symptoms the impairment in psychomotor performance continues for much longer, despite some recovery in blood pressure and return of cerebral

blood flow practically to baseline values. The finding of persistent impairment after a period of hypotension has parallels in the delayed return of the EEG to normal after defibrillation threshold testing (Singer *et al.* 1992b). It suggests that following return of normal perfusion some time may be required to restore tissue oxygen levels and to restore the biochemical equilibrium. This finding has important implications for patients who suffer from sustained and nonsustained ventricular arrhythmias and who operate machinery or continue to drive. The occurrence of even transient symptoms of cerebral hypoperfusion at the onset of an arrhythmia indicates the potential for significant psychomotor impairment which may persist for many seconds after the resolution of the symptoms.

PART II: AN ANALYSIS OF THE RISKS OF DRIVING IN PATIENTS WITH AN ICD. COMPARISON WITH THE RISKS IN OTHER GROUPS CURRENTLY ALLOWED TO DRIVE.

Scale of the problem:

A study of 1348 patients dying of coronary artery disease showed that 71 (5%) of these deaths occurred in patients who were driving (Myerburg & Davis 1964). Minor accidents resulted from 24 of these deaths, all without causing injury to third parties. A study of 9,330 sudden deaths (Bowen 1973) revealed that 98 (1%) occurred in people who were driving. Accidents (all minor) resulted from 47% of these deaths. These figures clearly place the problem of sudden incapacitation of drivers through coronary artery disease in context. Nonetheless it is clear that patients with ICD's are a group at particularly high risk of sudden incapacitation and any decision to allow such patients to drive must be based on a clear

review of the risks involved. The most reasonable way to do this is based on the assessment of the risk of a disabling episode occurring over time, expressed as the number of hours of exposure to the risk needed before such an episode will occur. This concept is well accepted in the world of aviation medicine where a figure of $1:10^6$ hours is accepted for private pilots and for commercial pilots flying a multi-crew aircraft (Joy 1992). Unfortunately the regulations on fitness to drive in the United Kingdom are not based on an analysis of this type. To enable a comparison with what is currently regarded as acceptable it is necessary to identify a group of patients at increased risk of incapacitation who are allowed to drive. Patients with epilepsy form such a group. The occurrence of an epileptic fit is probably more likely to result in complete disablement of the driver than the discharge of an ICD whether or not this is for a genuine arrhythmia. In Kou and colleagues series (Kou *et al.* 1991) only 15% of patients who received a shock therapy from their ICD were syncopal. The current regulations for drivers with epilepsy state that "If a person has been on the same drug regimen for more than two years and remained free from attacks, car driving may be allowed" (Espir 1985). A licence may be granted for up to three years but is subject to withdrawal for a period of two years following a further seizure or if there is a change in antiepileptic drug therapy. Some of the best information on the cumulative risk of recurrent seizures in epileptics on drug therapy comes from the Medical Research Council Antiepileptic Drug Withdrawal Study Group (1991). This study recruited patients with known epilepsy who had been free of seizures for two years and randomized them to continued drug therapy or to progressive withdrawal of therapy over a 6-month period. Figure 6.13 shows the Kaplan-Meier curves for survival free of recurrent seizure in the patients in whom drug therapy was withdrawn and those in whom it was not.

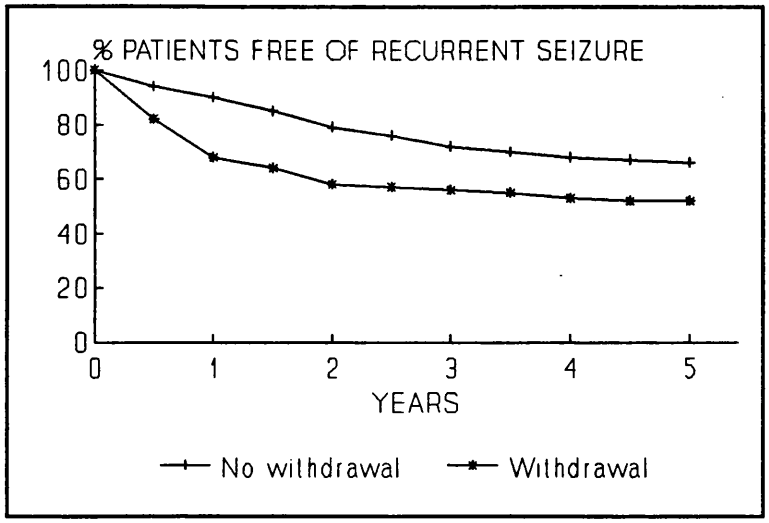

Figure 6.13: Survival free of recurrent seizure in patients epileptic patients whose drugs have been withdrawn versus those whose drugs were continued

It is noticeable that even in patients whose drugs are continued there is a significant ongoing rate of seizure recurrence despite it being over two years since the last seizure for all patients recruited. In the first year and second year after recruitment there was a 12% annual seizure recurrence rate falling to 9% in the 3rd year and 4% in the fourth year. If we assume that a 12% per annum level of seizure activity (which equates to a risk of $1:7x10^4$ hours) is the maximum regarded as acceptable then we can consider what groups or subgroups of ICD patients might have a lower incidence of device activity than this, based on the very conservative assumption that all device therapies result in syncope. The cumulative incidence of all therapies and shock therapies in our population of 47 patients is shown in Figure 6.14.

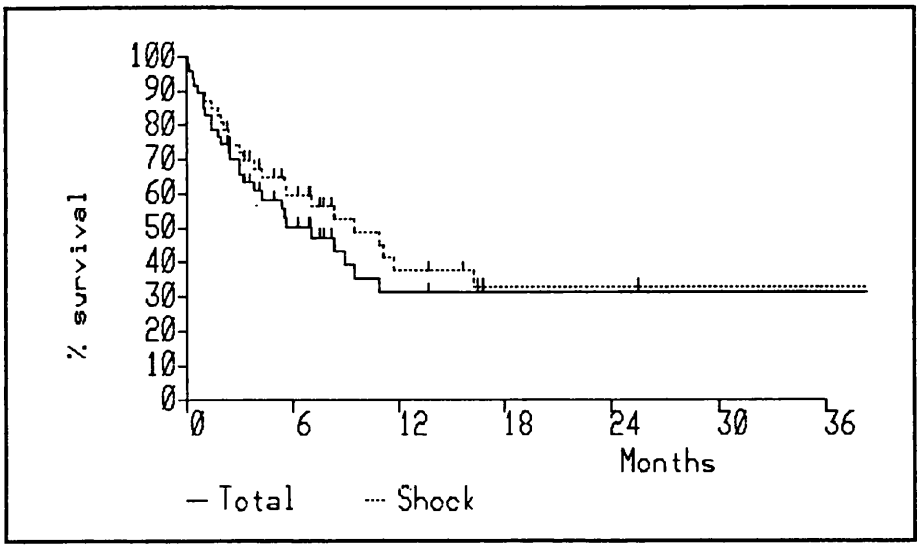

Figure 6.14: Survival free of shock therapies (Shock) and all therapies (Total) after ICD implantation

It is clear from this figure that the cumulative incidence of therapy delivery of 68% would preclude patients driving during the first year after ICD implant. Furthermore from our analysis of factors related to appropriate therapy in Chapter 4 no subgroup was identified with a first year shock incidence of less than 28%. These observations coincide with those from other studies of therapy delivery which show that between 40 and 70% of patients will receive a shock therapy in the year after ICD implant. However the dramatic reduction in the incidence of ICD therapy delivery in patients who have been free of ICD therapy in the 12 months after ICD implant is clear. No patient in our study received a therapy from their ICD who did not do so during the first twelve months after ICD implantation. These data identify the group of patients who have not received an ICD shock after one year as a possible low risk group for future therapy delivery. However, with the relatively small numbers in our study and the relatively short period of follow-up the confidence intervals for the survival curve at this point are wide. To make a more realistic assessment of the risk of therapy delivery after the first year it is necessary to consult data from larger published series.

Analysis of the risk of driving in patients who have yet to receive a therapy from their ICD:

Regrettably the large manufacturers databases have failed to collect information on time to first therapy delivery and there are very few published series where a sufficient number of patients have been followed for a long enough time to obtain useful data. Fogoros *et al.* (1989) published the first actuarial analysis of ICD therapy delivery and reported a cumulative incidence of therapy delivery of 51% at 12 months, 71% at 24 months and 81% at 48 months. Only 10% of the original population receive their first shock between 24 and 48 months after ICD implant. However these first therapies occur in the 29% of patients who have not received their first shock by 24 months and therefore represent an annual incidence of approximately 16%, which is above the acceptable risk figure of 12% which we have defined above. However this study was based on 65 patients with a mean follow-up period of 25 months so the number of patients followed over the 24 to 48 month period (which was not stated in the paper) must have been small. The data from a larger study of 188 patients (Griffith *et al.* 1988) and a similar study of 59 patients (Curtis *et al.* 1992) is shown in Table 6.3. These data suggest that even in an unselected population of ICD recipients the actuarial risk of a first ICD therapy falls below our 12% target from 2 years after ICD implant and possibly even earlier. Further data suggesting that at least some subgroups within the ICD patient population comes from the work of Levine and coworkers (Levine *et al.* 1991). They followed 197 patients with ICDs for 36 months and recorded therapy delivery. They stratified patients into subgroups on the basis of ejection fraction <25%, NYHA class ≥3, ß-blocker therapy and previous coronary artery bypass grafting. Cumulative survival in the various subgroups is shown in Table 6.4.

Table 6.3: Actuarial risk of first ICD therapy (from Griffith et al. 1988)

Years after ICD Implant	Actuarial Risk of ICD therapy (% per annum)	
	Griffith *et al.* 1988 (n=188)	Curtis *et al.* 1992 (n=59)
1	37	42
2	27	9
3	7	9
4	9	-
5-6	10	-

Table 6.4: Probability of survival free of ICD therapy (from Levine et al. 1991)

EF<25% & NYHA ≥ class III	ß-blocker	CABG	MONTHS 12	24	36
No	Yes	Yes	0.84	0.78	0.75
No	Yes	No	0.73	0.63	0.58
No	No	Yes	0.72	0.62	0.57
No	No	No	0.54	0.41	0.35
Yes	Yes	Yes	0.71	0.61	0.57
Yes	Yes	No	0.53	0.40	0.34
Yes	No	Yes	0.52	0.39	0.33
Yes	No	No	0.29	0.17	0.13

Shaded numbers indicate groups where the incidence of first therapy delivery in the previous 12 months is less than 12%.

Regrettably it is not possible to reconstruct the raw data for the whole population from this grouped data as the number of patients in each group is not given by the authors. However these data provide confirmation that the risk of ICD therapy in the second year after ICD implant remains too high to allow patients to drive. However, in patients who do not receive a shock in these first two years and who have ejection fractions greater than 25% and are not in NYHA grade 3 or 4 then the subsequent risk of an ICD discharge is below our 12% per annum target figure. Because patients with low ejection fractions and poor functional status are much more likely to receive an ICD therapy (Chapter 4, page 110) they represent a small proportion of patients free of therapy at two years and since their annual risk of ICD therapy at this point is 20% or less they may probably be ignored. In the same way patients with epilepsy who have risk factors placing them at higher risk of recurrent seizure even after two years free of seizures can be identified (Medical Research Council Antiepileptic Drug Withdrawal Study Group 1993) but are not excluded from driving under present regulations because they represent a small proportion of the whole population and have a small impact on the overall risk of allowing such patients to drive.

Analysis of the risk of driving in patients who have already received a therapy from their ICD:

There is very little published data on the actuarial occurrence of further therapies after the initial occurrence of an ICD therapy. Of the 27 patients in this thesis who have received an ICD therapy (appropriate, inappropriate or both), 22 (81%) have subsequently received another therapy at least one week after the first therapy. Griffith *et al.*(1988) published data on the actuarial occurrence of second therapy delivery in the years following first therapy delivery and these data are summarised in Table 6.5. This table shows that in all subsequent years the incidence of further ICD therapy is 25% or above, suggesting that patients who

have already received an ICD therapy should not be allowed to drive (with the possible exception that therapy delivery was inappropriate and due to a hardware failure such as sensing lead fracture).

Table 6.5: The actuarial incidence of a second ICD therapy following first therapy delivery (From Griffith et al. 1988)

Years after ICD Implant	Actuarial Risk of ICD therapy (% per annum)
1	39
2	33
3	31
4	25

Discussion:

The prime factor in deciding whether ICD patients may drive must be considerations of public safety. Whilst a blanket ban on driving in ICD patients may be the easiest way to ensure this it may impose unreasonable restrictions on a minority of ICD patients. With an increasing volume of data on the cumulative occurrence of therapy in ICD patients it is possible to propose an alternative strategy. It is clear from the data presented in this thesis and that of many published studies that no group can be identified with a sufficiently low incidence of therapy delivery in the first year after ICD implant to make it reasonable for them to drive. Currently available data suggests that this ban should be continued for the second year after ICD implant pending the availability of more data. For the third year free

of therapy and onwards there is evidence that the risk of ICD therapy is sufficiently low to make driving acceptable particularly in certain lower risk subgroups with good functional status and ejection fraction above 25%. Because the incidence of ICD therapy is lower in these groups they form the vast majority of patients free of therapy delivery by two years anyway. In our population just under 50% of patients fall into this lower risk group and about 70% of these remain free of therapy delivery after two years so around a third of ICD recipients would be likely to be eligible for a driving licence at this time. Additionally the mean age of this subgroup is 42 years compared with 49 years for the other patients and their employment prospects may suffer more as a result of not being able to drive.

If such patients were to be allowed to drive and suffered a further therapy episode they would again have to surrender their licence. The very limited data currently available on the occurrence of second therapy delivery suggests that these patients should remain banned from driving. However it is worth noting that the data on which this statement is based was collected from all patients who had received an ICD therapy rather than those who had been free of an ICD therapy for two years prior to their first ICD therapy. In other words a group which is at low risk of a first therapy delivery may have a subsequent low risk of a second therapy delivery, which might allow these patients to reapply for a licence after a further period free of therapies. Further data is required before a policy based on risk analysis can be adopted for these patients.

It is clear from our psychomotor study that the occurrence of episodes of nonsustained ventricular tachycardia without symptoms or with symptoms of palpitations alone is not associated with significant psychomotor impairment and should not on its own result in the loss of a driving licence. This decision should be made on the probability of a syncopal arrhythmic episode occurring. Conversely patients in whom nonsustained arrhythmias are associated with even transient hypotensive symptoms should have their driving licence

withdrawn as our study shows clear evidence of prolonged impairment of psychomotor function even with transient (<5 seconds) symptoms.

The one remaining question is how patients who have episodes of ventricular tachycardia reliably treated by antitachycardia pacing should be treated. Clearly patients with even transient haemodynamic symptoms associated with the ventricular tachycardia should have their licence withdrawn, even if the arrhythmia is successfully terminated by pacing therapy. In patients who have arrhythmias not associated with haemodynamic symptoms the possibility of tachycardia acceleration is the overriding concern. At electrophysiological study the incidence of acceleration has been reported to be between 0 and 36% depending on the pacing cycle length but automated therapies delivered from the ICD appear to be associated with a low acceleration rate of around 3% (Wietholt *et al.* 1993). In our population the apparent incidence of tachycardia acceleration by defibrillator therapies has been very low although precise identification of episodes of acceleration is not easy with all of the ICDs we have used. A more substantial problem may be of failure of the pacing therapy to terminate the arrhythmia allowing the ICD to proceed to cardioversion therapies. No substantial account of the impact of ICD therapy delivery on patients engaged in activity has been published and the risk analysis described above is based on the assumption that any therapy delivery from the device necessarily disables the recipient. This is certainly not the case with all ICD patients. More data from large scale prospective studies is required to enable the implementation of driving regulations for all ICD patients based on a rational assessment of risk.

Conclusion:

The current ban on driving by ICD recipients is a source of considerable inconvenience and may result in loss of employment. The ban was implemented at a time when there was

insufficient data to formulate a rational policy with regard to ICDs and driving and it is ripe for review.

Review of the current regulation concerning epilepsy and driving suggests that the maximum accepted level for recurrent seizures is approximately 12% per annum. Making the very conservative assumption that any therapy delivery from an ICD would necessarily result in immediate disablement it is clear from our own data and that from other series that patients who receive an ICD should have their driving licence withdrawn for a period of two years. Following this they should be able to reapply for their licence provided that they have not received a therapy (appropriate or inappropriate) from the device. This licence should again be surrendered if they receive a further therapy from the device although in future it may be possible to reissue the licence after a further shock-free period or if they have episodes of arrhythmia which have been repeatedly and reliably terminated by antitachycardia pacing therapy. Because of the availability of data logging patient concealment of recurrent arrhythmia episodes is not a problem. The occurrence of episodes of ventricular tachycardia associated with even transient symptoms, whether self-terminating or terminated by antitachycardia pacing should also disqualify the patient for a two-year period. However episodes of nonsustained ventricular tachycardia which are asymptomatic or associated with palpitations alone are not grounds for withdrawal of the licence.

On the basis of our study findings and a review of the published data such a policy represents a reasonable compromise between the overriding need for the safety of the general public and the needs and desires of ICD recipients.

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CHAPTER 7:

IMPLICATIONS FOR PRESENT AND FUTURE APPLICATIONS OF THE IMPLANTABLE CARDIOVERTER DEFIBRILLATOR RESULTING FROM THE USE OF A SIMPLE MODEL OF COST-EFFICACY:

Introduction:

Since the first implant in man of an ICD in 1980 the number of devices implanted annually has roughly doubled each year (Nisam *et al.* 1991b). By the end of 1991 over 20,000 devices had been implanted worldwide (Nisam *et al.* 1992) with probably 80% of these implants occurring in the USA. In 1990 the total number of patients who had received an ICD in the United Kingdom was 40 (Griffith *et al.* 1990b) and this has risen to approximately 360 at present (Nathan AW *personal communication*). These figures suggest a per capita implant rate of around 5% that of the USA.

One factor which has limited the more widespread use of the ICD within the United Kingdom has been the high initial cost of the device (£10,000 - £18,000). The ICD has been perceived as an expensive therapy because of the capital cost of this single item, which cannot easily be accommodated within existing budgets. This may however represent an unfair comparison with other therapies where the costs may be the same or greater but more widely dispersed within departmental budgets and over many years. Much of the published data on the cost of ICD therapy comes from the United States. During the period of this study the exchange rate has fluctuated between 1.5 and 2.0 US$ to the pound sterling. An intermediate rate of £1.00 = US$1.75 has been used for conversion in this study.

Organised attempts to assess the cost-efficacy of medical interventions are relatively rare. However, in the light of the perceived expense of ICD therapy three groups have considered its cost-efficacy. Kupperman *et al.*(1990) produced a figure of US$17,400 (£10,000) per life-year saved (1986 prices) but their model suggested this could fall to $7,400 (£4,200) per life-year by 1991 as a result of increased defibrillator longevity and reduced hospital stay. These figures suggested the ICD is equivalent in cost-efficacy to many other medical therapies (Table 7.1).

In the United Kingdom O'Brien *et al.*(1992) has used a similarly complex model to assess the cost-efficacy of the ICD in comparison with long-term amiodarone therapy. Their model studied a 20 year period using extrapolated survival data from a variety of studies (Winkle *et al.* 1989a, Herre *et al.* 1989) and produced a cost-efficacy range of £10,000 to £20,000 per life-year reducing with technical and implantation developments to £6,000 per life-year.

In a simple study which considered only the in-hospital costs of ICD use O'Donoghue and colleagues (1990) have demonstrated a 20% saving associated with the early implantation of the ICD when compared with more extensive evaluation of antiarrhythmic drug therapy followed by ICD implantation if no effective drug therapy could be found. Although this study does not consider the overall cost-efficacy of these two approaches it does serve to highlight the importance of considering costs other than those of the ICD itself when addressing the issue of cost-efficacy.

Most recently Larsen *et al.*(1992) used a Markov "state transition" model to compare the cost-efficacy of the ICD with that of amiodarone therapy and produced a marginal cost-effectiveness of $29,200 per life-year for the ICD versus amiodarone therapy.

Whilst they are elegant and sophisticated approaches to the assessment of ICD cost-efficacy none of the four studies described above provides a simple method to assess the cost-efficacy of the ICD using different survival data or costs. They highlight the need for a simple, flexible cost-efficacy model which may be used to assess new and existing strategies

Table 7.1: Cost-efficacy comparison of the ICD (Kupperman *et al.* 1990). Figures corrected to 1986 prices.

Procedure	Cost-efficacy: US$ per Life-Year
Hospital Haemodialysis	59,500
Coronary artery bypass grafting for severe angina (single vessel disease)	44,200
Heart Transplantation	26,900
Treatment for mild hypertension	23,200
ICD (1986 Scenario)	**17,400**
Treatment for severe hypertension	11,100
ICD (1991 Scenario)	**7,400**
Coronary artery bypass grafting for three-vessel disease	7,200

for implantable defibrillator use. Such a model should be capable of using locally derived costing and survival data to maximise the relevance of its output. To this end a simple model of the cost-efficacy of the ICD was developed and applied to a wide variety of data from published studies to assess the cost-efficacy of ICD use in a variety of circumstances.

Methods:

The cost-efficacy calculation used in our model is based on the simple equation:

$$\text{COST-EFFICACY} = \frac{\text{TOTAL COST OF ICD USE IN THE POPULATION}}{\text{GAIN IN LIFE-YEARS IN THE POPULATION}}$$

Cost-efficacy is expressed as Cost (in pounds sterling) per Life-Year (£/LY). This is the amount of money which must be spent to give one patient one extra year of life. No adjustment is made for the quality of this life as only a few small studies (Vlay *et al.* 1989, Keren *et al.* 1991, Kalbfleisch *et al.* 1989) have so far considered this aspect of implantable defibrillator use. Because of the limited availability of long-term survival data for ICD recipients a fixed time period has been used for the calculation. This period is assumed to be three years except where otherwise stated.

In calculating the total cost of ICD use we take the cost of identifying the patient at risk (screening tests), the cost of the hospital stay required for ICD implantation, the cost of the implantation surgery, the cost of the ICD generator and leads, and the cost of follow-up over the life of the generator. These costs are written off over the three year period of the study. Subsequent generator replacement costs are not considered.

To calculate the gain in years of life accruing from the use of the ICD in any particular population a simple calculation is performed. Figure 7.1 shows the survival curve for a hypothetical population of 100 subjects in which the sudden death mortality is 16% in the first year, 8% in the second year and 4% in the third year. If the defibrillator prevents all the sudden deaths over the 3-year predicted ICD generator life then 16 patients who would have died during the first year will gain a mean additional survival of 2.5 years (assuming sudden deaths are evenly distributed through the year) giving a total gain of 40 life-years. A similar calculation can be performed for the second and third years. However patients who die as

a result of ICD implantation actually lose life-years and this must also be taken into account. Their deaths also reduce the number of life-years gained by the rest of the population. Knowing the cost for 100 defibrillator implants and follow-up over the three year period and the net gain in life-years the cost per life-year can be calculated.

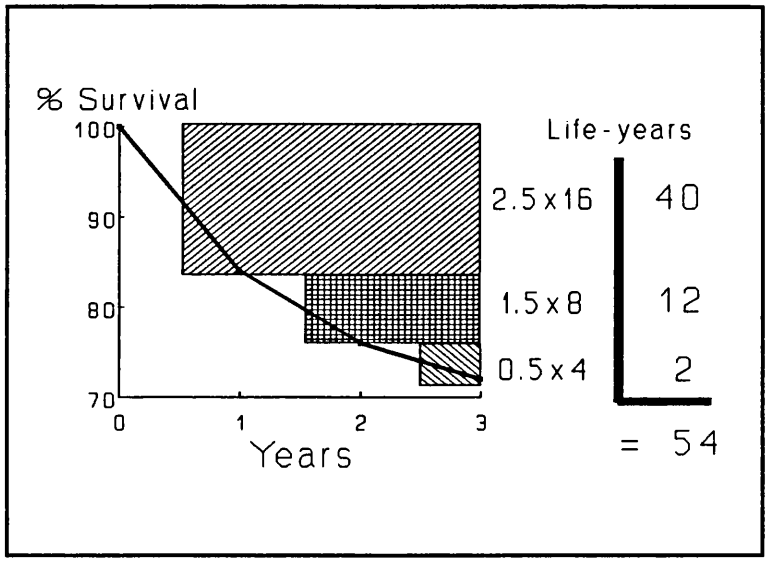

Figure 7.1: Method of calculation of gain in Life-Years. The dark line shows the untreated survival free of sudden death in a hypothetical population of 100 patients. The shaded boxes represent the gain in Life-Years accruing if the ICD prevents all sudden deaths. The total gain of 54 Life-Years calculated is reduced to 52.4 years $(54 \times \frac{100-3}{100})$ *as the 3% of the population who die gain no benefit from the ICD. In addition the 3 patients each lose a potential 3 Life-Years (totalling 9 Life-Years) so the final gain from the strategy is 43.4 Life-Years*

The cost assumptions which have been used in our model are shown in Table 7.2. These are based on 1991 prices and have been derived from a number of sources. The single most expensive item at any ICD implant is the ICD generator itself. The purchase cost of an ICD generator in the United Kingdom currently varies between £5,000 for a simple defibrillation-only device without Holter or data logging functions to £15,000 for a third generation device with bradycardia support pacing, antitachycardia pacing, low energy cardioversion and data

Table 7.2: The costing assumptions used in our costing model (1991 figures)

ITEM		COST(£)
SCREENING TESTS	Echocardiogram	55
	Signal average ECG	50
	Holter recording & analysis	100
Limited electrophysiological study (VT stimulation)		500
Repeat VT stimulation study		150
ICD generator		10,000
ICD leads (including patches and pace sense leads)		1,650
ICD implantation surgery cost (O'Brien *et al.* 1992)		3,200
Additional hospital stay (day charge)		265
Follow-up visit (6 in first year and 4 in subsequent years)		100

logging facilities. Marked variations in the cost of ICD models can occur depending on the manufacturers view of their current position within the market. The figure of £10,000 which we have used in our model allows the purchase of a modern device without antitachycardia pacing but with data logging/Holter functions. The ICD also requires the purchase of pace/sense electrodes and epicardial patches (two or three) or transvenous electrode(s) with or without an axillary patch electrode. Although the costs of individual components of these systems vary quite markedly between manufacturers the total cost of a complete lead system

is remarkably similar. Our figure of £1,650 reflects the cost (at 1991 prices) of the electrodes used in the first 14 epicardial implants performed at this hospital. Duration of surgery for epicardial ICD implantation has been similar to that for coronary artery bypass surgery and although the amount of disposable equipment used at ICD implants is less the additional cost of technicians and cardiology staff means that the cost of the two procedures is similar. We have not attempted a detailed cost-analysis of ICD implantation surgery cost but have taken a figure of £3,200 for surgical implantation using epicardial patches. This figure represents the 1991 cost of a coronary artery bypass procedure and includes a 24 hour stay on a high dependency unit postoperatively. This figure is derived from that used to charge for procedures performed on patients from outside our region and includes the cost of staff, equipment and maintenance of facilities. Our figure accords closely with that quoted in O'Brien's study (O'Brien *et al.* 1992). Similarly the bed cost for additional nights is that charged to cover staff, equipment, drug and building costs in 1991.

The cost of screening tests and electrophysiology studies have been derived from figures calculated in 1990 and adjusted to 1991 prices to allow for cross-charging between the Medical School and hospital. All charges include staff time, the cost of equipment depreciated over a two year period and the costs of ancillary services such as heat and light. Follow-up visits have been costed on the basis of a three-monthly follow-up routine with two additional unscheduled visits allowed for in the first year and assuming that 10% of visits require a day-case admission for full evaluation of defibrillator function.

Many of the cost assumptions which we have used may differ in other institutions. A major advantage of our simple model is that it can readily adapt to any alteration of the baseline costing assumptions.

Applications of the Costing Model:

We have applied the model to examine three aspects of the cost-efficacy of ICD use:

- ICD use in survivors of out-of-hospital cardiac arrest.
- ICD use strategies proposed by the current generation of controlled trials.
- The impact of technical and surgical developments on the cost-efficacy of ICD use.

The main purpose of our model is to examine the relative cost-efficacy of various strategies of ICD use. Whilst it is of great interest to know how the cost-efficacy of ICD use compares with other therapies care must be taken in making such comparisons using data from our simple model. The methodology used by other investigators is more complex and designed to produce an absolute figure for cost-efficacy. It often includes an adjustment for quality of life and economic discounting of future years survival. For general comparison Table 7.3 shows the cost of other medical therapies (Williams 1985) adjusted for inflation to 1991 prices..

Costing the Use of the ICD in Cardiac Arrest Survivors:

Survivors of an out-of-hospital cardiac arrest occurring in the absence of acute myocardial infarction are a heterogenous group. Wilber *et al.*(1988) described the long-term outcome when this group is subdivided on the basis of electrophysiological testing combined with measurement of left ventricular ejection fraction. He stratified patients into subgroups based on whether they had high (>30%) or low (≤30%) left ventricular ejection fraction, whether

Table 7.3: Cost-Efficacy of Medical and Surgical Procedures from Williams (1985) corrected to 1991 figures.

PROCEDURE	Cost £/Life-Year
Pacemaker for Complete Heart Block	1120
Hip replacement	1200
Valve replacement for aortic stenosis	1440
Coronary artery bypass grafting for three-vessel disease	2040
Kidney transplant	4800
Heart transplant	8000
Hospital haemodialysis	17600
Coronary artery bypass grafting for single-vessel disease	19300

(These prices include an element for quality of life and may not be directly comparable with those from our model).

arrhythmias were inducible at electrophysiological study and whether these arrhythmias were rendered noninducible by antiarrhythmic drug therapy (Figure 7.2).

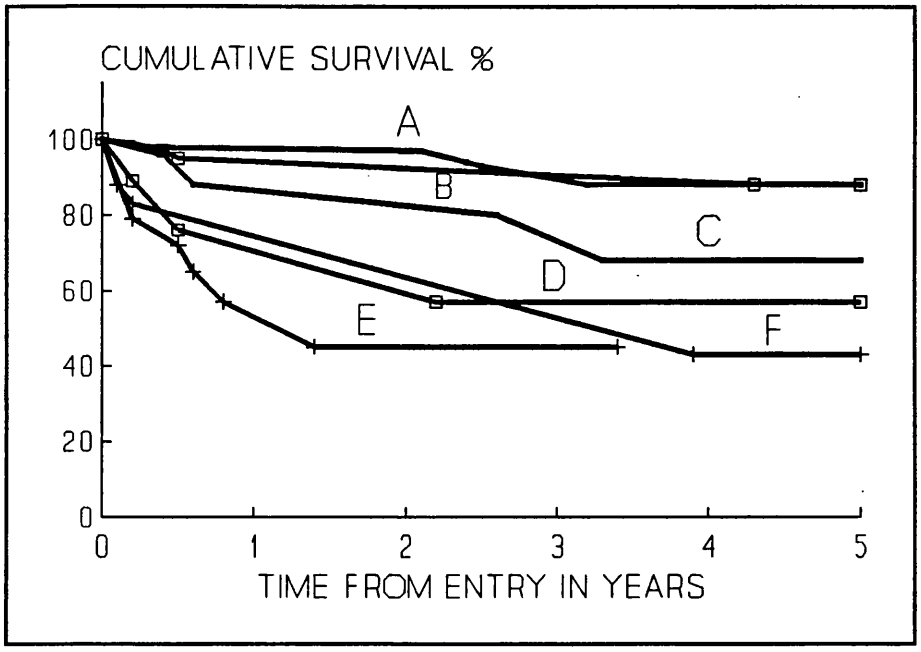

Figure 7.2: Plot of cumulative survival free of recurrent cardiac arrest for cardiac arrest survivors: (Group A - Inducible arrhythmia, suppressed by drugs, high EF; Group B - Noninducible, high EF; Group C - Inducible arrythmia, suppressed by drugs, low EF; Group D - Noninducible, Low EF; Group E - Inducible arrythmia, not suppressed by drugs, low EF; Group F - Inducible arrhythmia, not suppressed by drugs, high EF). Modified from Wilber et al.(1988)

By using our model in combination with the survival data from this study we have calculated the cost-efficacy of ICD use in each of Wilber's subgroups, in the whole population and in various combinations of subgroups. (Figure 7.3). The cost-efficacy of ICD use ranges from £22,400 per life-year in the highest risk subgroup (Ejection fraction ≤30%, inducible arrhythmia, not suppressed by antiarrhythmic drug therapy) to nearly £700,000 per life-year in the lowest risk subgroup (Ejection fraction >30%, no inducible arrhythmia). Whilst ICD use in the highest risk subgroup appears very cost-effective such a strategy will have little impact on the overall incidence of sudden death, as only 27% of recurrent cardiac arrest incidents occur in this subgroup. By contrast, a policy of general ICD implantation in all

cardiac arrest survivors is more expensive (£57,000 per life-year) but could potentially prevent all sudden cardiac deaths. Comparison with the cost of other medical therapies (Table 7.3) suggests that this is an expensive strategy.

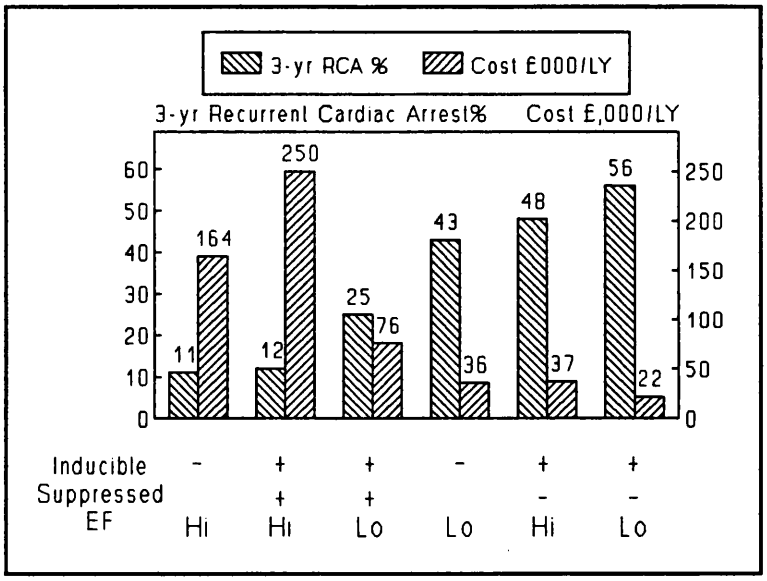

Figure 7.3: Three-year recurrent cardiac arrest (RCA) incidence and cost of ICD use in thousand pounds per life-year in the six groups shown in Figure 7.2

A combined approach using the ICD in the three subgroups at highest risk of recurrent cardiac arrest {(a) Inducible nonsuppressed low ejection fraction, (b) inducible nonsuppressed high ejection fraction, (c) noninducible low ejection fraction} increases the potential for prevention of sudden death as 56% of recurrent cardiac arrests occur in this group. This increased yield in the combined high risk group can be gained for a marginal rise in cost to £23,600 per life-year.

In the light of O'Donoghue's finding that early ICD implantation is associated with reduced hospital costs we have used our model to assess the cost-efficacy of a more simple approach to selection of patients for ICD implantation using either baseline inducibility at

a single electrophysiological study or ejection fraction alone. A single electrophysiological study costs £500 and may involve one or two extra days in hospital. In Wilber's group 79% of patients had an inducible arrhythmia and 86.2% of recurrent cardiac arrests occur in this group. However, because of the cost of using an electrophysiological study to identify this large group at relatively low risk of sudden death the cost per life-year of this strategy is £57,000. This is identical to that of using no screening test at all and appears to offer no advantage over such a policy. By contrast measurement of ejection fraction is cheap and involves no extra hospital stay. The low ejection fraction subgroup comprises 33% of the population and 52% of recurrent cardiac arrests occur in this subgroup. The cost-efficacy of ICD use in this subgroup alone is £25,500 per life-year which is a considerable improvement when compared to ICD use in the whole population (£57,000 per life-year). However despite the shorter hospital stay this approach is less cost-effective than use of the ICD in the combined high risk group described above and would prevent a smaller proportion (52% versus 56%) of the total number of sudden deaths.

Our costing model suggests that generalised use of the ICD in all cardiac arrest survivors is an expensive strategy. The cost-efficacy may be improved by restricting ICD use to subgroups at higher risk of sudden death. The model suggests that a combination of ejection fraction measurement and electrophysiologic assessment is superior in identifying a cost-effective high risk subgroup than either of these investigations alone.

The relationship between cost-efficacy and yield of sudden death prevention for various strategies is illustrated in figure 7.4.

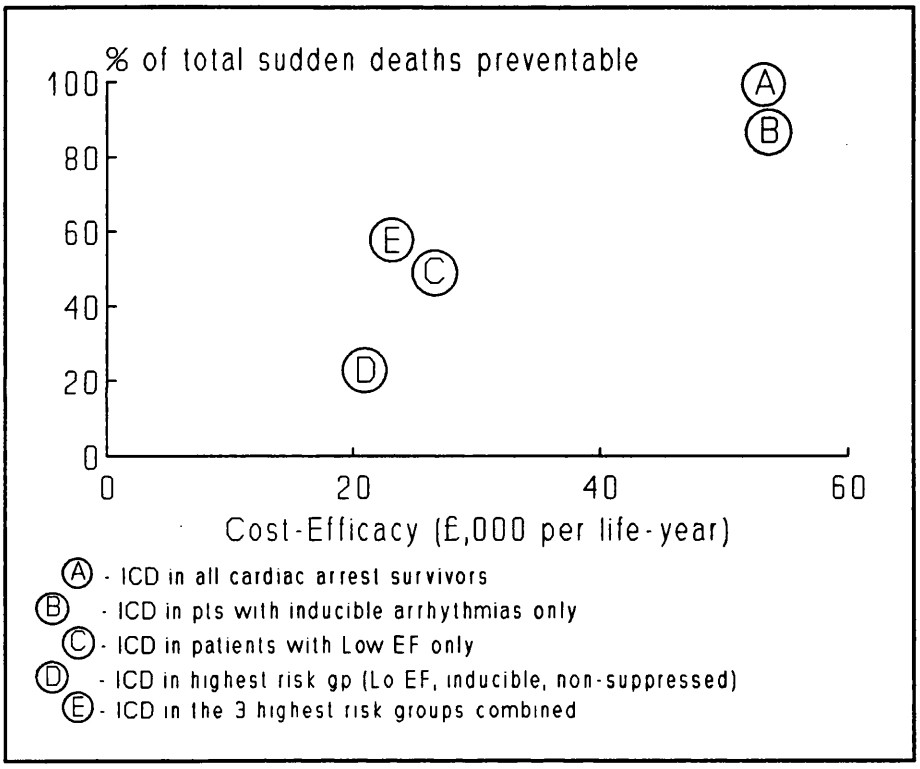

Figure 7.4: Relationship between cost-efficacy and yield of prevention of sudden death for a variety of selection strategies

A number of studies are in progress to compare ICD use in cardiac arrest survivors with conventional electrophysiologically-guided drug therapy. The Dutch Prospective Study (Wever & Hauer 1992) is specifically addressing the issue of cost-efficacy. The results of these should enable a more rational use of the ICD in these patients.

Costing Future Applications of the ICD:

A large number of controlled trials of the ICD are currently planned or under way (Nisam *et al.* 1991a, Bigger 1991). Amongst these trials are a number which aim to evaluate new risk groups for ICD implantation. These include patients with nonsustained ventricular tachycardia, high risk patients after myocardial infarction, patients undergoing coronary

artery bypass grafting and patients with severe dilated cardiomyopathy awaiting cardiac transplantation.

Using the costing model we have assessed the cost-efficacy of the strategies proposed by these trials using published survival data for the various groups at risk.

ICD cost-efficacy in patients with Nonsustained Ventricular Tachycardia:

Three separate trials of the use of the ICD in patients with nonsustained ventricular tachycardia (NSVT) and known coronary artery disease but without a history of sustained VT or VF are in progress. The MADIT study (Multicenter Automatic Defibrillator Implantation Trial) recruits patients with NSVT who have inducible arrhythmias at baseline electrophysiological study which remain inducible on procainamide (MADIT executive committee 1991). These patients are randomized to ICD or "conventional" drug therapy. MUSTT (Multicenter Unsustained Tachycardia Trial) and SDPS (Sudden Death Prevention Study) both compare EP-guided drug therapy with placebo for patients with inducible arrhythmia. In the EP-guided patients the ICD is used for patients who remain inducible despite drug therapy. The rationale for these studies is that the presence of inducible arrhythmias at electrophysiological study correlates closely with subsequent VT or VF (Denniss *et al.* 1986, Richards *et al.* 1987) and that patients with NSVT have a high incidence of inducible arrhythmias and these patients in turn have a high incidence of sudden death (Wilber *et al.* 1990, Kadish *et al.* 1990)

Wilber *et al.*(1990) have published data on survival free of cardiac arrest for patients with coronary artery disease, left ventricular ejection fraction <40% and nonsustained ventricular tachycardia. They have stratified this population by inducibility of sustained ventricular tachycardia at electrophysiological study and whether such tachycardias could be suppressed by antiarrhythmic drug therapy. The results of this stratification are shown in Figure 7.5.

Using these data and our model the strategy of ICD use proposed by the MADIT trial costs £42,600 per life-year and the strategy of the MUSTT and SDPS trials cost £23,500 per life-year. This cost-efficacy is similar to that gained by using the ICD in cardiac arrest survivors. However worrying reports of difficulty with recruitment for the MADIT trial suggest that the prevalence of inducible arrhythmias noted in the Wilber study (43%) may not be representative of this group as a whole. This would increase the number of patients who need to be screened to find one patient at risk and reduce the cost-efficacy of this strategy.

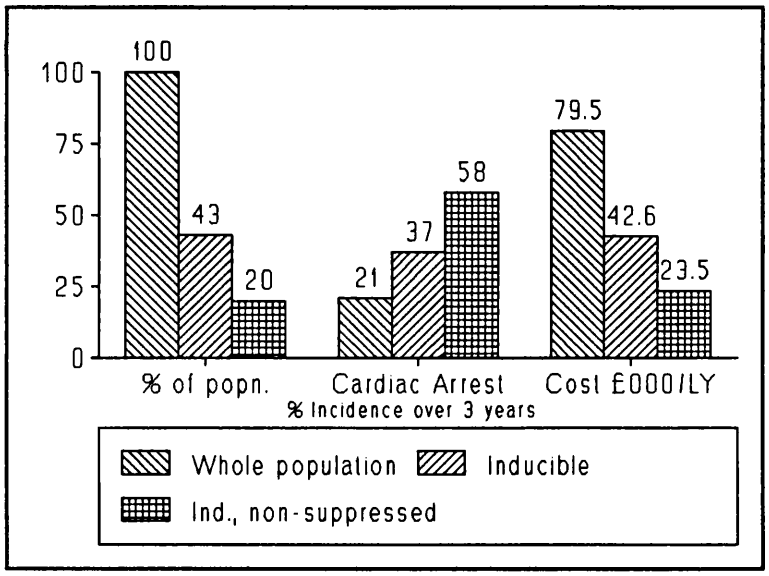

Figure 7.5: Stratification of patients with nonsustained ventricular tachycardia using the costing model and data from Wilber et al.(1990)

ICD cost-efficacy in patients at high risk following Myocardial Infarction:

Survivors of myocardial infarction represent a large population who are known to be at increased risk of sudden cardiac death. Much interest has centred on the identification of

subgroups of this population who are at particularly high risk. Although electrophysiological studies have been reported to be effective at identifying patients with a high risk of recurrent cardiac events (Richards *et al.* 1991) most interest has focused on the use of noninvasive screening tests. At St. George's Hospital we have a large database of myocardial infarction survivors. Over 500 patients have now been followed for three years or more and the population has been studied for predictors of sudden death. Currently the best group of tests to identify patients at high risk appear to be the combination of reduced heart rate variability, more than 10 ventricular ectopic beats per hour and a positive signal-averaged ECG (Farrell *et al.* 1991). At three years this population has a sudden death mortality of 29.9% in comparison with 4.5% for the population as a whole and 7.5% for those patients with an ejection fraction less than 40% (Figure 7.6).

The cost of ICD use in this high risk population with a 29.9% 3-year sudden death rate is £36,500/life-year which is less than twice that of using the device in highest risk subgroup of cardiac arrest survivors. However whilst this group may be approaching an acceptable level of cost-effectiveness it includes only 26% of the patients who will die suddenly in this period and this represents only 10.5% of the total deaths. Extending the use of the ICD to the larger group with an ejection fraction of less than 40% (which contains 38% of the population) increases the cost nearly five-fold to £170,000 per life-year. The overall impact of ICD use on post infarction mortality is likely to remains small unless the sensitivity and specificity of screening tests for patients at risk of sudden death improves. The ACTAID (Australasian Clinical Trial of the Automatic Implantable Defibrillator) study which evaluates the implantation of the ICD in patients with inducible arrhythmias post-infarction is in the early stages of recruitment and should provide valuable data on the role of the ICD in survivors of myocardial infarction.

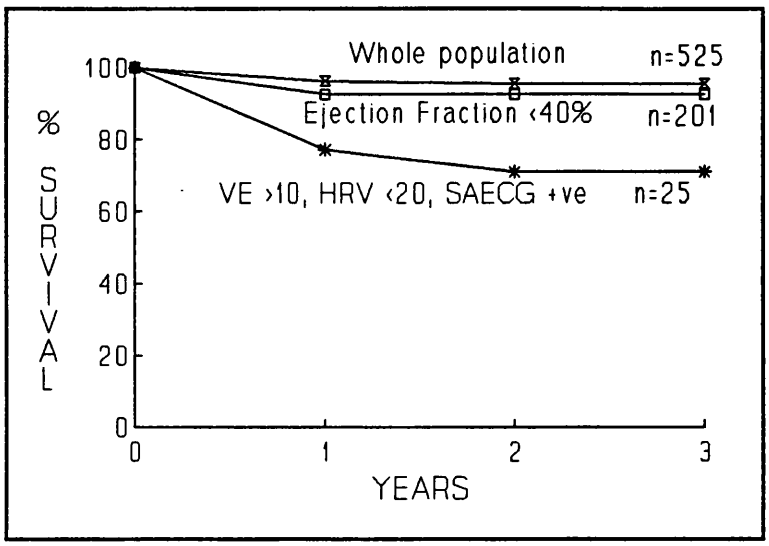

Figure 7.6: Stratification of myocardial infarction survivors using data from the St. George's Hospital database. A high risk group of patients with frequent ventricular extrasystoles, reduced heart rate variability and positive signal-averaged ECG have a 29.9% three-year mortality from sudden death

ICD cost-efficacy in patients with Low Ejection Fraction and Positive Signal-Averaged ECG:

The "CABG Patch" study is already in progress (Bigger 1991). It recruits patients already destined for coronary artery bypass grafting (CABG) with impaired left ventricular function (ejection fraction <35%) and a positive signal-averaged ECG (SAECG). Patients are randomized to CABG or to CABG plus ICD. Insertion of the ICD at the same time as CABG surgery saves on both surgical and bed stay costs for implantation.

There are no published survival data for an identical group but the study is apparently based on a retrospective study of these patients by the investigators (Nisam *et al.* 1991a) which showed an unexpectedly high mortality. Data is available for a similar group of patients with a positive signal-averaged ECG and ejection fraction of less than 40% (Gomes *et al.*

1987). The one-year mortality in this group appears to be about 12-14%. Extrapolation is required to produce a three-year sudden death mortality of 21% so that the costing figure of £44,000 per life-year is subject to wide confidence limits. Using data from the post-infarction database at St. George's Hospital suggests that patients with an ejection fraction <35% and a positive SAECG have a three-year sudden death rate of just 4.2%. This produces a very high cost of £570,000/life-year. However the patients in the St. George's database do not necessarily require coronary artery bypass grafting and might therefore be presumed to be at lower risk of sudden death than those entering the "CABG patch" study. Clearly it is not possible to make any definitive conclusions about the strategy proposed by this trial pending the availability of survival data from the trial itself.

ICD cost-efficacy in patients awaiting Cardiac Transplantation:

About 40% of deaths from congestive heart failure are thought to be of an arrhythmic nature (Packer 1985, Francis 1988) and patients with dilated cardiomyopathy awaiting cardiac transplantation appear to be at particularly high risk of sudden death (Stevenson *et al.* 1987). This has given rise to the suggested use of the ICD as a bridge to transplantation (DEFIBRLAT = Defibrillator Implantation as Bridge to Later Transplantation (Bolling *et al.* 1990)) although the protocol of this study has yet to be published. Stevenson *et al.*(1987) found a 34% one-year sudden-death mortality in the group with an ejection fraction <25% and the mortality rose to 57% in those patients with a stroke volume of less than 40ml. In these patients our costing model was adjusted to assume a one-year wait to transplantation with a 50% 5-year survival following transplantation. Because of the high mortality and short follow-up period in this group the defibrillator appears highly cost effective (£16,000/life-year in the whole group and £9,300/life-year in the high risk group). However, it must be remembered that these costs are additional to the cost/life-year of the transplant itself.

EXPENDITURE IMPLICATIONS OF THE STRATEGIES PROPOSED BY THE CURRENT GENERATION OF CONTROLLED ICD TRIALS:

We have already seen that the cost-efficacy of the various controlled trials of the ICD varies markedly. By calculating the approximate numbers of patients in the various risk groups we can calculate the expenditure implications for the United Kingdom of the adoption of the strategies proposed by the trials. The current population of the United Kingdom is 57 million and the annual incidence of myocardial infarction is estimated at 4 per 1,000 population (Petch 1989) giving an annual total of approximately 225,000 of whom about 135,000 survive (Tunstall-Pedoe *et al.* 1975). The basic cost of each ICD implant alone (without any allowance for screening test or follow-up costs) is £16,700. If we restrict ICD use only to those patients with reduced heart rate variability, a positive SAECG and increased ventricular ectopic beats we would need 6420 ICDs per annum at an approximate cost of £107 million.

It is hard to make an accurate assessment of the number of survivors of out-of-hospital cardiac arrest in the UK because there is no central registry for such events. A study of out-of-hospital defibrillation conducted in Scotland (Cobbe *et al.* 1991) would produce a figure of just under 4,000 if the findings are extrapolated to the whole United Kingdom. A figure of 8.3 cardiac arrest survivors per 100,000 population was produced by a study in rural Iowa (Stults *et al.* 1984) and extrapolation to the United Kingdom gives a figure of just under 5,000 per annum. We have used the figure of 4,000 in our calculations. Assuming we give all of these patients an ICD the annual expenditure required for implantation alone would be £67 million/annum. If we restrict the ICD to those with a low ejection fraction then this figure is reduced to £22 million/annum and if we use the ICD only in the highest risk group with low ejection fraction and inducible nonsuppressed arrhythmias the cost falls to £8 million/annum.

In patients with nonsustained ventricular tachycardia we can assume that such patients are selected from the 135,000 patients who survive a myocardial infarction. In the St. George's study group 5% of such patients had nonsustained ventricular tachycardia on Holter monitoring. If we restrict ICD use to the highest risk group with inducible tachycardias (like the MUSTT and SDPS trials) not suppressed by conventional antiarrhythmic drug therapy the annual cost would be £22 million/annum. If we adopt the broader strategy of device use in all patients with an ejection fraction below 40% and inducible ventricular arrhythmias (like the MADIT trial) the cost rises to £48 million/annum.

In 1989 295 coronary artery bypass operations were performed in the United Kingdom per million of the population (Unger 1991) giving a total of 16,800 procedures. Our own database suggests that 5.7% of these would have positive signal-averaged ECG and reduced ejection fraction which would qualify them for the CABG patch trial. If such a policy was adopted in the UK the annual cost would be £16 million.

Approximately 400 heart transplants were performed in the United Kingdom in 1990. If we were to restrict ICD use to the group at highest risk of sudden death (Ejection fraction <25% and stroke volume <40ml) the cost would be just £2 million/annum. By contrast, if the ICD was used in myocardial infarction survivors the additional expenditure required would be massive. Even to implant solely in a selected high risk group (which contains just 5% of infarct survivors) would cost £107 million/annum and have a very limited impact on overall mortality.

All of the strategies proposed by the current generation of ICD trials (with the exception of DEFIBRLAT) have considerable implications for national expenditure on cardiology (Table 7.4). These findings emphasise the need for careful costing to be an integral part of these and future studies of the ICD.

Table 7.4: Annual expenditure implications for the United Kingdom of adopting the strategies proposed by the various controlled trials of the ICD.

RISK GROUP		Number of patients	Annual Cost £
CARDIAC ARREST SURVIVORS	All patients	5000	$67x10^6$
	Low EF	1670	$22x10^6$
	Inducible, nonsuppressed, Low EF	585	$8x10^6$
Nonsustained VT	i.e. MADIT	2900	$48X10^6$
	i.e. MUSTT and SDPS	1350	$22x10^6$
SAECG positive + low EF (i.e. CABG patch)		970	$16x10^6$
Dilated Cardiomyopathy awaiting transplant (i.e. DEFIBRLAT)		150	$2x10^6$
ICD use post myocardial infarction (High risk group)		6420	$107x10^6$

EF - ejection fraction; MADIT - Multicenter Automatic Defibrillator Implantation Trial; MUSTT - Multicenter Unsustained Tachycardia Trial; SDPS - Sudden Death Prevention Study; DEFIBRLAT -Defibrillator Implantation as Bridge to Later Transplantation.

FUTURE TECHNICAL DEVELOPMENTS IN THE ICD AND SCREENING TESTS:

The costing scenarios considered above have been based on a number of assumptions which are likely to change over the next few years. Using our costing model we have assessed the impact of these developments in our high risk post-myocardial infarction group where the cost per life-year is currently £36,500. Use of the ICD in this group currently appears relatively expensive when compared to other accepted medical therapies.

Increased generator life:

If we assume an increase in generator life to 5 years and that the sudden deaths are distributed so that two-thirds of them occur in the first 3 years after ICD implantation the cost of ICD use in our high risk post-infarction group falls to £25,000 per life-year. The relationship between generator life and cost-efficacy is illustrated in Figure 7.7. Further extensions of generator life beyond five years are likely to have a relatively small impact.

Generator price reduced:

Assuming a 50% reduction in the real cost of a simple defibrillator the cost of ICD use in our high risk post-infarction group falls to £28,000 per life-year. The relationship between generator price and cost-efficacy is shown in Figure 7.8. It is interesting to note that even if the ICD generator was free the cost of this strategy would still be £19,500 per life-year.

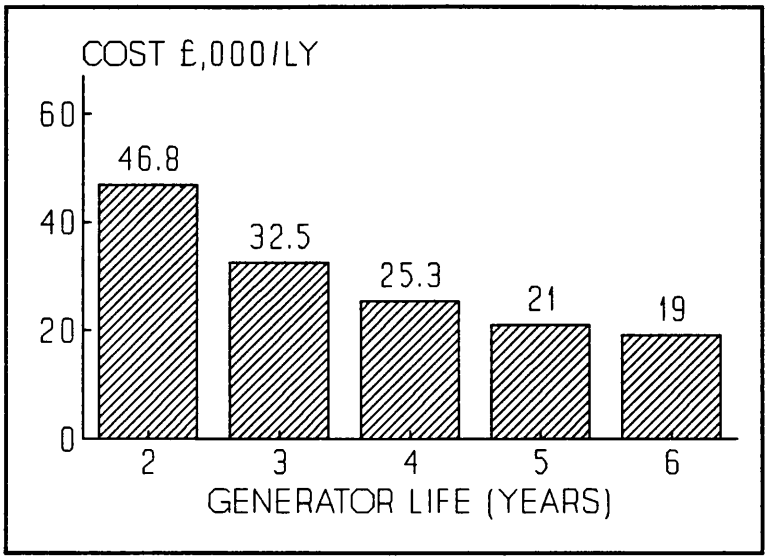

Figure 7.7: The effect of increasing generator life on the cost-efficacy of ICD use in a hypothetical population with a 3-year sudden mortality of 28%

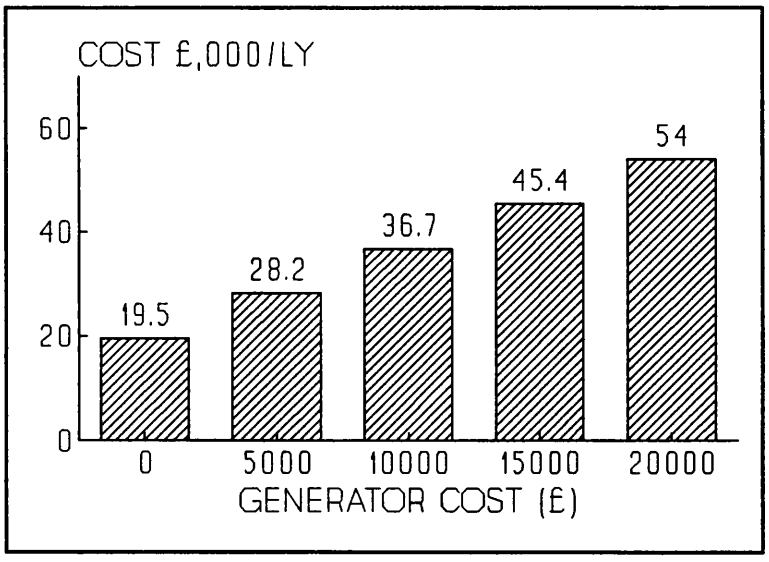

Figure 7.8: The effect of changing generator cost on the cost-efficacy of ICD use in survivors of myocardial infarction at high risk of sudden cardiac death

Transvenous Implantation:

Transvenous implantation is likely to be associated with shorter hospital stay and reduced cost of implantation surgery. However the cost of the defibrillator is unchanged and most transvenous lead systems are marginally more expensive than their epicardial counterparts. Calculation of cost-efficacy on this basis alone produces only a marginal improvement in cost-efficacy to £32,000 per life-year. A more important means by which transvenous implantation may improve cost-efficacy is by reducing the mortality associated with ICD implantation. The exact scale of this reduction remains to be determined but the study of Lehmann *et al.* suggested a reduction from 4.7% to 1.6%. The potential improvement in cost-efficacy which could result if implant mortality is reduced, particularly in groups whose annual sudden death mortality is relatively small, is graphically illustrated in Figure 7.9.

Screening tests:

Despite considerable effort improvements in screening tests to identify patients at high risk of sudden death have been slow and not always reproducible in different centres. However the interest in screening test improvement is understandable when the economic effects are considered. A screening test able to detect a group with a three-year sudden death rate of 60% would improve cost-efficacy to £18,000 per life-year. However, any new screening test must be relatively cheap as well as being sensitive and specific. Figure 7.10 shows the relationship between screening test cost and the size of the population at risk identified by the test. For a population such as ours, where the risk group represents approximately 5% of the population screened a screening test should not cost more than £250 per patient.

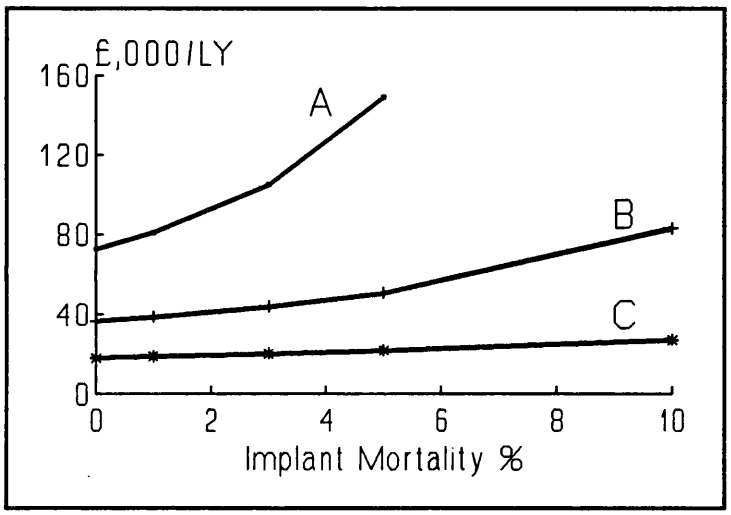

Figure 7.9: The effect of altering implant mortality on the cost-efficacy of ICD use is illustrated in three populations with differing three-year sudden death rates: A) 14% B) 28% C)56%. The improvement in cost-efficacy from improved implant related mortality is greatest where the use of the ICD is marginal i.e. where sudden death mortality is low

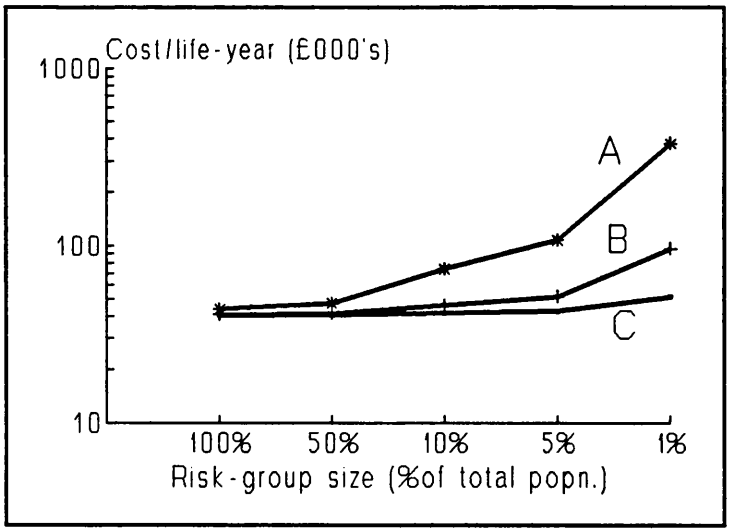

Figure 7.10: The effect of different screening test costs (A - £50, B - £250, C - £1500) on cost-efficacy in relation to the size of the group selected by the test. The smaller the high risk group selected, the more sensitive it is to screening test cost

Combined future scenario:

A combined future scenario with a halved generator cost, five-year generator life, transvenous implantation with 1.5% implant mortality and improved screening test would cost just £7,700 per life-year, a reduction of over 75% in the current cost. Changes of this magnitude would have a dramatic effect on the perception of the ICD as an expensive therapy.

OTHER FACTORS OF IMPORTANCE IN THE ASSESSMENT OF COST-EFFICACY:

Nonsudden and noncardiac death:

Patients remain at risk of death from nonarrhythmic mechanisms even after insertion of an ICD. The rate of nonarrhythmic death may have an important influence on the cost efficacy of the implantable defibrillator. It is clear from large series (Nisam *et al.* 1991b) of ICD patients that the nonsudden death rate considerably exceeds that due to sudden cardiac death and this reflects the efficacy of the ICD in preventing sudden cardiac death. The nonsudden death rate appears to be between 6 and 14% per annum (Levine *et al.* 1991, Zilo *et al.* 1991, Axtell *et al.* 1991, Palatianos *et al.* 1991) and there has been much interest in identifying factors which predict a higher risk of death. Some authors (Levine *et al.* 1991) have found that concurrent CABG reduces subsequent mortality whilst others (Klein *et al.* 1991) have not. Similarly it is remains unclear whether ICD shock delivery is or is not an independent predictor of subsequent mortality.

Using our model we have examined the effect of varying levels of nonsudden mortality and the hypothesis that ICD shock delivery is associated with patients at increased risk of nonsudden death on the overall cost-efficacy of the ICD in two hypothetical populations (Figure 7.11).

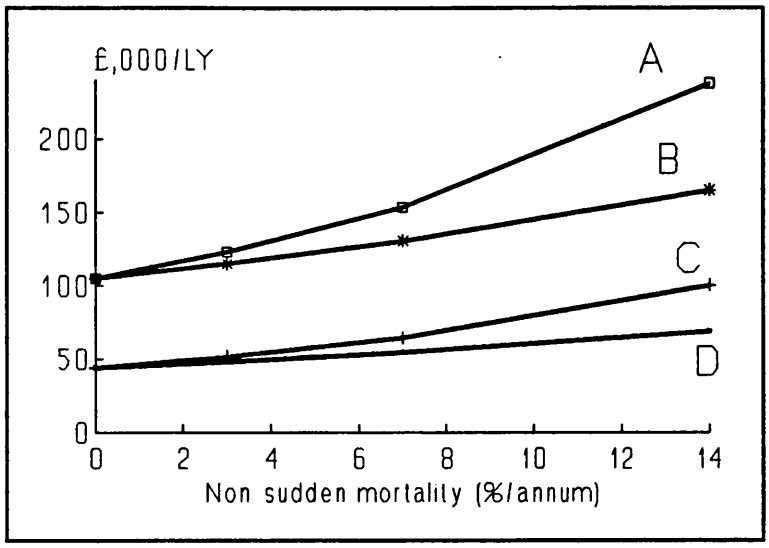

Figure 7.11: The impact of nonsudden mortality on cost-efficacy. Lines B & D show the impact of altering nonsudden mortality in ICD patients with a 14% and 28% three-year sudden death mortality. Lines A & C show the impact of the same nonsudden mortality with the assumption that patients who receive an ICD therapy have a doubled risk of subsequent nonsudden mortality

Efficacy of the ICD in preventing sudden cardiac death:

It is clear that the ICD will not prevent every sudden arrhythmic death as there will be a small number of device or lead failures or devices which are inactive. Most studies (Winkle *et al.* 1989a, Winkle *et al.* 1991, Fogoros *et al.* 1987) have reported an annual incidence of sudden arrhythmic death of around 2% in patients with the ICD but Gross *et al.*(1991a) studied 56 ICD patients and found that the cumulative survivals free of sudden death was 93% at 1 year, 89% at 3 years and 75% at 5 years suggesting the figure is nearer 7-8%/annum. A reduction in device efficacy has a predictable effect on cost efficacy. A reduction of device efficacy to 50% doubles the cost per life-year saved. Even assuming that

the figures of Gross are more representative than those of the other studies then the error in our calculated cost-efficacies would still be less than 10%.

Discussion:

Sudden cardiac death remains a public health problem of massive proportion in the Western world with probably 70,000 sudden deaths/annum in the United Kingdom alone. Despite the availability in some communities of cardiopulmonary resuscitation by bystanders and out-of-hospital defibrillation less than one in three patients suffering a cardiac arrest are resuscitated and survive to hospital discharge (Weaver *et al.* 1986). About two-thirds of cardiac arrest victims have some form of cardiac disease recognised before the terminal event and the potential exists to identify those at risk of sudden cardiac death in advance. However, until the development of the ICD there was little incentive to do so. The dramatic increase in the frequency of implantation of the ICD illustrates the perception of need for such a device. Initial retrospective studies suggested that the device was highly efficacious in preventing sudden cardiac death. This observation has made the ethics of performing a randomised controlled trial of ICD use in cardiac arrest survivors very difficult. However no such dilemma affects the study of the prophylactic use of the ICD in patients with no previous history of cardiac arrest but a high risk of sudden cardiac death in the future. Hence the large number of studies of prophylactic ICD use currently planned or under way.

However the expansion in the use of the ICD has not been entirely uncriticised and attention has been drawn to the expense of the device (Campbell 1990). Similar criticisms were made in the early days of the heart transplantation programme in the UK (O'Brien *et al.* 1987) and were addressed by a detailed study of the costs and benefits of the technique (Buxton *et al.* 1985).

The question of the cost-efficacy of the ICD was first considered by Kupperman *et al.*(1990) using decision analysis techniques. They used data from the 1984 Medicare data base, the medical literature, Medicare carriers, individual pharmacies and hospitals and expert opinion to estimate the cost of ICD therapy versus the cost of conventional therapy in a group of patients with at least one episode of cardiac arrest not associated with myocardial infarction. This study concluded that the cost of ICD use in cardiac arrest survivors was well within the range of costs for other life-saving interventions in the U.S.A. at that time and that the real cost of ICD therapy would halve by 1991. The main limitation of this elegant study is the difficulty of knowing exactly how the costing and survival figures in the study were derived. Because of the transatlantic differences between health care systems it is very difficult to know how applicable the findings are to ICD use in the United Kingdom.

Recently Larsen *et al.*(1992) have published a sophisticated analysis comparing the cost-efficacy of amiodarone and ICD use. They used a complex "state transition" decision model to determine the outcome of each population and to calculate the costs incurred. This is a very sophisticated model which attempts to account for all possible costs incurred by patients in each group (for example the costs associated with the side-effects of amiodarone). The marginal cost-efficacy of amiodarone over conventional therapy was $6,600 per life-year and the marginal cost-efficacy of the ICD compared with amiodarone was $29,200 per life-year. Sensitivity analyses were conducted to examine the impact of prolonging generator life and of alterations in the quality of life on amiodarone or ICD therapy. Prolongation of generator life to five years improved ICD cost-efficacy to $16,500 per life-year.

The cost-efficacy of using the ICD in Britain in comparison to long-term amiodarone therapy was considered by O'Brien *et al.*(1992). Their model studied a 20 year period using economic modelling and approximated life-expectancy data from a variety of studies and produced a range of cost-efficacies depending on the survival data used for the amiodarone

treated and ICD treated groups. No comparison was made with the cost-efficacy of other accepted medical therapies but the authors again suggested that technical and implantation developments could improve cost-efficacy two or three-fold.

Whilst these three studies represent sophisticated and elegant attempts to assess the cost-efficacy of the ICD their complexity makes their application to assess alternative applications of the ICD difficult. To facilitate such comparisons and to enable the impact of various strategies on the cost-efficacy of ICD use to be assessed we have developed a simple model in which the total cost of ICD use is divided by the gain in life-years to produce a cost per life-year figure. By substituting locally derived cost-figures and using our simple method to calculate the gain in life-years the model may easily be applied to a wide range of different situations. We have applied the model to study the cost-efficacy of a number of current and possible future indications for ICD use. Unlike the more complex studies described above our model does not assume any savings in drug therapy and no assumptions are made about subsequent hospital admissions. Reliable data from large scale studies on these variables is not yet available but there is as yet no evidence that the ICD reduces subsequent drug costs or frequency of re-hospitalisation.

Our model assumes 100% prevention of sudden cardiac death by the implantable defibrillator and any deviation from this will increase the cost per Life-Year saved. Most studies have suggested that the incidence of sudden cardiac death in ICD recipients is very low (Winkle *et al.* 1989a, Winkle *et al.* 1991, Fogoros *et al.* 1987). An adjustment for altered efficacy is easy to include in our model when the gain in Life-Years is being calculated. A similar adjustment can be performed to assess the effect of varying nonsudden death rates in different groups of patients. High nonsudden mortality rates also reduce the gain in Life-Years from ICD use and impair cost-efficacy accordingly.

A recurring finding during our study has been the trade-off which occurs between improving cost-efficacy and reducing the yield of prevented sudden death. That such a trade-

off occurs reflects the relatively poor sensitivity and specificity of current screening tests for patients at risk of sudden cardiac death. The model also illustrates the dramatic improvement in cost-efficacy which can occur if screening tests become more specific. Screening tests must also be cheap enough not to have a significant impact on the cost-efficacy of ICD use in the selected high risk group. Paradoxically, as the high risk group selected by the test become smaller the cost of the screening test becomes more and more important in determining overall cost-efficacy of ICD use.

A number of trials of the prophylactic use of the ICD are in progress or planned. Our model strongly suggests that the cost-efficacy of all of these strategies lies within a narrow range. This range lies only slightly above the range of cost-efficacies for the current widely accepted use of the ICD in cardiac arrest survivors which in turn is slightly above that of a number of relatively expensive therapies provided by the National Health Service. The adoption of any of the prophylactic strategies for ICD use in the United Kingdom would require substantial additional expenditure because of the large number of patients involved.

However the assumptions used in the calculation of these figures are rapidly being overtaken by technical improvements, competitive pricing and improved implantation techniques. Combinations of such factors will have a very powerful effect to reduce the cost of ICD use and may result in an improvement in cost-efficacy of up to five-fold over the next few years which could dramatically alter the perception of the ICD as an expensive therapy.

As more reliable data on the efficacy of the ICD become available from prospective randomised controlled trials the findings of this study this study can be refined, particularly as many of the clinical trials in progress are directly measuring the cost of the various treatment strategies under test. Modelling of future cost-efficacy will continue to have an important role for health care planners and in helping to direct future medical research.

Conclusion:

A flexible model of the cost-efficacy of ICD use has been developed and used to examine a variety of strategies and the impact of technical and medical developments. The implantable cardioverter defibrillator appears at present to be a relatively expensive means of preventing sudden death and the cost-efficacy is surprisingly similar for many different applications which are currently being considered for the device. Technical and medical developments are likely to cause a dramatic reduction in the cost of using the device over the next few years but to make a significant impact on the overall incidence of sudden death large numbers of patients will have to be treated and this will demand substantial provision of medical and financial resources. Modelling the cost-efficacy of new medical interventions may prove a useful way to identify those factors which have an important effect on cost-efficacy and those which do not. Careful application of this information may enable more rational provision and use of scarce resources.

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CHAPTER 8

OVERVIEW AND CONCLUSIONS

Sudden Cardiac Death and the ICD

Sudden cardiac death is one of the major causes of death in the Western world. At least 80% of these deaths occur due to coronary artery disease although only a proportion are due to acute myocardial infarction. In the remainder a ventricular arrhythmia occurs as a result of transient ischaemia or due to myocardial abnormalities dating from previous myocardial infarction. The ICD has been developed to reduce the incidence of sudden cardiac death and although randomised controlled studies of its efficacy are lacking the results of this study and of other published work suggest that it is an effective therapy. However the risks associated with ICD therapy and its high cost mean that it is only sensible to use the device in patients at high risk of sudden cardiac death in the future. Although technical developments are likely to reduce both the risks and the true cost of ICD therapy this limitation will remain for the foreseeable future. Thus the current position of ICD therapy is this. We have identified a condition (sudden cardiac death) and we have a therapy which is effective in preventing this condition (the ICD). Unfortunately when the condition presents it is too late to apply the therapy and therefore the primary need is for reliable tests to identify the patient at risk of sudden cardiac death. In patients who have presented with a previous cardiac arrest this study and others have identified left ventricular function and possibly the results of electrophysiological study as a means by which patients at particularly high risk may be identified. However the majority of sudden cardiac death victims do not receive a "second chance" by being resuscitated and considered for ICD therapy. The major issue therefore remains identifying patients who are at risk but have not yet suffered a cardiac arrest. A large

number of randomised trials of the ICD are under way in groups thought to be at high risk (such as patients with nonsustained ventricular tachycardia, inducible ventricular arrhythmia and low ejection fraction). Unfortunately our cost-efficacy analysis suggests that our ability to identify such patients sufficiently cheaply to make widespread ICD use a reality may be limited. Although some combinations of risk factors (such as those described by Farrell (1992) for myocardial infarction survivors) can identify patients at high risk with reasonable specificity their sensitivity is poor. Although the use of the ICD in these patients appears to approach accepted levels of cost-efficacy the overall reduction in the burden of sudden cardiac death in the population achieved by this strategy is small. Thus there is a need for screening tests with higher sensitivity and specificity if the overall impact of the ICD on the incidence of sudden cardiac death is to be improved. No test or combination of tests currently under evaluation offer such a possibility and there remains the worrying possibility that there may be a stochastic element to the occurrence of sudden cardiac death which will render more sensitive and specific identification of potential victims impossible.

Transvenous Defibrillation systems

If widespread implantation of the ICD is to become an accepted therapy it is unlikely to do so until the requirement for a thoracotomy has been abolished. Additionally the cost-efficacy analysis conducted in this thesis confirms that implant mortality is a significant factor in determining the cost-efficacy of ICD use, particularly in patients where the risk of sudden cardiac death is relatively low. For both these reasons it was clear from the early days of implantable defibrillation system that the development of a transvenous defibrillation system was desirable. The use of superior vena cava spring electrodes was shown to be associated with higher defibrillation thresholds than a pure epicardial patch system in the early days of implantable defibrillator use. Because of the relatively low energy output (25 joules or less)

available from early defibrillators the overriding need was to obtain the lowest defibrillation thresholds and epicardial systems predominated. However with the rapid development in devices energy outputs improved and transvenous electrode system were again considered. Between 1989 and 1992 we evaluated three manufacturers versions of these systems, usually with the addition of a subcutaneous patch in the axilla because of concerns over energy requirements and stability of purely transvenous defibrillation leads. All of these systems delivered monophasic shocks and a consistent finding with all systems was that a defibrillation safety margin defined by multiple defibrillation successes at a fixed energy level of 18-20 Joules was satisfied at approximately 70% of implants. Our study reveals that no single variable is sufficiently powerful to reliably identify patients in whom this threshold will not be met. However the most powerful variable in this respect proved to be heart diameter in centimetres measured from the posteroanterior chest X-ray. No other variable contributed significantly to the identification of these patients. The rapid development and increasing availability of devices capable of delivering biphasic shock therapies seems likely to revolutionise the use of transvenous electrodes by lowering defibrillation thresholds and thus increasing the percentage of patients in whom transvenous lead systems may be used. The results of this study provide an interesting starting point for the analysis of factors which may be associated with the failure of lead only defibrillation system using biphasic shock to meet the defibrillation safety margin.

The chronic performance of implantable defibrillators remains an important issue. Some of the patients in whom these devices are implanted have life expectancies in the absence of sudden cardiac death in excess of ten years. If these patients are to achieve a good quality of life the need for revision of the defibrillation system must be minimised. The analysis of pacing, sensing and defibrillation in this thesis suggests that the performance of transvenous defibrillation systems will at least match that of currently available epicardial systems. However the relatively high incidence of lead displacement must be addressed and a low

incidence of lead fracture must be demonstrated. It is possible that the smaller ICDs of the future will be implanted in the pre-pectoral position. The shortened subcutaneous course of the defibrillation lead may reduce the mechanical stresses on them, and hence the incidence of fracture and displacement.

Quality of Life in ICD patients

It is essential if the ICD is to be more widely used for the prevention of sudden cardiac death that its use is acceptable to patient and physicians alike. The cumulative incidence of inappropriate therapy delivery in our series was 29% at 24 months. Inappropriate therapy delivery may be dangerous and can have serious adverse psychological effects. Our study failed to identify any underlying clinical factor associated with the delivery of inappropriate therapies and their occurrence is primarily a reflection of the limited diagnostic capabilities of the current generation of implantable cardioverter defibrillators. It remains a substantial challenge to develop an improved sensing algorithm for the ICD capable of improving specificity without reducing the sensitivity of detection of life threatening ventricular arrhythmias.

A major source of complaint from all our ICD recipients was that current regulations prevent them from driving a motor vehicle. This prevents some of them from pursuing their employment and is of great inconvenience to over 80% of our patients who were active drivers prior to receiving an ICD. Our analysis suggests that the current regulations are inconsistent in that they allow patients with epilepsy to drive who may be at considerably higher risk of sudden disablement than certain subgroups of implantable defibrillator recipients and that a conservative policy would be to allow patients who had been free of shock therapies from the device to reapply for a driving licence after two years subject to a review of their future risk by their physician.

Future Research Directions

This study highlights the need for future research in many areas. The most important is unquestionably the study of the natural history of conditions associated with sudden death and the improved identification of patients at high risk of sudden cardiac death. There is clearly a need for the continuing collection of data on the performance of implanted defibrillation systems which is only partly satisfied by manufacturers databases, which suffer from under reporting of complications and an inherent conflict of interest. The evolution of national and multinational databases of implanted devices is of critical importance. Such databases should collect cost and performance data so that the true cost-efficacy of ICD therapy in various groups of patients may be established. This will enable us to establish the correct position for the ICD in the armamentarium of cardiac therapies.

Criticisms

The most serious criticism of this thesis must be the small number of patients on which its conclusions are based. This reflects the slow development of ICD use in the United Kingdom and occurs despite St. George's being one of the top two implanting centres in the United Kingdom. This limits the use of statistics to analyse the results, particularly in subgroups of the main population. However the different composition of this population in comparison with those in large implanting centres in the United States and the fundamental difference of referral (or lack of referral) practices in the United Kingdom mean that data from large studies conducted elsewhere may not necessarily be extrapolated to this country and even such small studies provide fresh insight. The data in this study also has the advantage of being collected almost entirely by the author and is thus free of the differences of

interpretation which may occur with multiauthor multicentre studies. Of course this study has had to evolve with ICD implantation at St. George's and no doubt had I known the way this would develop at the start of the study some things (for example defibrillation threshold testing) might have been investigated in greater detail and analysed differently. Nonetheless this thesis contributes to the broad understanding of the risks and benefits of ICD therapy with transvenous electrode systems, and to our understanding of the economics and social consequences of ICD therapy.

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Anderson MH, Paul VE, Jones S, Ward DE. Transtelephonic interrogation of the implantable cardioverter defibrillator. PACE 1992;15:1144-1150

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APPENDIX A: Variables used in the analysis of defibrillation threshold at implant

Case	1<20J			Presentation				Causation	
No.	1≤20J 2>20J	Age at implant	EF	Arrest	SustVT	Other	CAD	Myop	Other
1	1	34.07	30	3	0	0	0	1	0
2	1	62.73	61	1	0	0	0	0	1
3	1	66.61	25	0	27	0	1	0	0
4	1	63.88	15	1	2	0	1	0	0
5	1	59.51	35	0	1	1	0	1	0
6	1	22.24	62	1	0	10	0	0	1
7	1	40.19	75	2	0	0	0	0	1
8	1	47.49	70	1	0	0	0	0	1
9	1	48.86	41	0	10	0	0	1	0
10	1	52.28	72	2	0	0	0	1	0
11	1	52.99	58	0	1	0	0	0	1
12	1	39.24	75	0	6	0	0	1	0
13	1	53.49	45	1	0	1	1	0	0
14	1	53.68	25	0	2	0	1	0	0
15	1	63.52	71	0	0	5	1	0	0
16	1	32.79	71	1	1	0	0	1	0
17	1	38.30	58	1	0	0	0	0	1
18	1	16.24	69	1	0	0	0	0	1
19	1	15.99	55	1	0	0	0	0	1
20	1	23.28	58	1	1	1	0	0	1
21	1	17.12	74	2	0	5	0	0	1
22	1	29.20	58	1	0	0	0	0	1
23	1	63.84	53	2	0	0	0	1	0
24	1	53.71	66	0	0	5	0	1	0
25	1	58.01	48	3	0	0	1	0	0
26	1	33.53	28	1	0	0	0	1	0
27	1	17.05	83	1	0	0	0	1	0
28	2	56.60	30	1	2	0	1	0	0
29	2	56.88	70	1	1	0	0	1	0
30	2	51.94	28	0	1	0	0	1	0
31	2	66.15	40	1	0	0	1	0	0
32	2	52.58	31	1	0	0	1	0	0
33	2	50.84	12	2	0	0	1	0	0
34	2	69.86	37	0	13	0	1	0	0
35	2	51.05	70	1	0	0	0	0	1
36	2	65.62	72	3	0	0	1	0	0
37	2	30.52	8	0	5	0	0	1	0
38	2	74.71	54	0	4	0	1	0	0
39	2	65.60	32	0	8	0	0	1	0

Appendix A cont;

				Endocardial wire			
Case No.	Amio at implant	Amio level	DEA	Threshold	R-wave	Inducible	Drug trials
1	1	0.7	1.1	0.8	10	1	6
2	0	0.5	0.8	0.5	8	0	0
3	1	1.4	1.5	0.5	15	1	7
4	0	1.1	1.2	0.8	11.2	1	4
5	0	0	0	0.4	8.6	0	0
6	0	0	0	0.7	9	0	1
7	0	0	0	*	8.4	0	0
8	1	0.9	0.8	0.6	20	0	0
9	0	0	0	0.2	9.6	1	5
10	0	0	0	0.7	18	0	0
11	0	0	0	0.8	12	0	0
12	0	0	0	0.6	10.8	1	5
13	0	0	0	1.6	9.6	1	4
14	1	2.3	2	0.3	7.3	1	1
15	1	0.2	0.1	0.4	18.6	0	5
16	0	1.1	1.2	0.9	9	1	4
17	0	0	0	0.5	7.2	0	0
18	0	0	0	0.3	15	0	0
19	0	0	0	0.5	10.1	0	2
20	0	0	0	0.5	7.1	1	2
21	0	0	0	0.4	8	0	0
22	0	0	0	0.4	9.2	0	0
23	0	0	0	0.4	18.7	0	0
24	0	0	0	0.2	12.9	0	0
25	1	1.1	0.8	0.5	14.2	0	1
26	0	0.8	0.7	0.7	10.3	0	1
27	0	0	0	0.6	8.3	0	0
28	0	0	0	0.2	12.6	1	6
29	1	1.6	0.9	0.5	7.4	0	5
30	0	0	0	0.8	3	1	3
31	1	2	1.4	1.2	19.2	1	1
32	0	0.8	0.6	0.7	19.8	1	2
33	0	1.9	1.1	0.9	15.6	1	2
34	1	0.3	0.8	0.7	11	1	4
35	0	0	0	0.1	11.4	0	0
36	0	0	0	0.1	16	0	0
37	0	0.6	0.8	1.1	13.5	1	3
38	1	1.2	1	0.1	24.5	1	5
39	0	0.1	0.1	0.6	9	1	6

* = missing data

Appendix A cont;

Case No.	Weight kg	Height cm.	BSA m2	LVEDD	CTR	Heart Diam	Chest Diam	Type 1 AAD
1	72	173	1.96	5.7	0.5781	18.5	32	0
2	65	159	1.74	5.9	0.5286	18.5	35	0
3	75	166	1.88	4.7	0.5161	16	31	0
4	69	178	1.98	7.2	0.5469	17.5	32	0
5	67	172	1.87	5.3	0.5	14.5	29	0
6	56	169	1.63	4.8	0.5	13.5	27	0
7	92	175	2.13	4.7	0.4688	15	32	0
8	102	174	2.18	5.3	0.4706	16	34	0
9	74	172	1.95	4.5	0.5625	18	32	1
10	75	170	1.93	5	0.4688	15	32	0
11	89	175	2.12	6.2	0.5294	18	34	0
12	67	169	1.84	5.5	0.5645	17.5	31	0
13	94	170	2.08	7.7	0.5156	16.5	32	0
14	80	164	1.92	8.4	0.5758	19	33	0
15	61	177	1.86	5.8	0.5161	16	31	0
16	72	169	1.9	5	0.4516	14	31	0
17	63	162	1.74	5.2	0.463	12.5	27	0
18	64	160	1.72	4.8	0.4483	13	29	0
19	50	158	1.56	5.2	0.4615	12	26	0
20	67	184	2	4.2	0.4667	14	30	0
21	57	162	1.67	4.1	0.4717	12.5	26.5	0
22	74	169	1.93	5.8	0.5323	16.5	31	0
23	72	169	1.98	6.5	0.5833	14	24	0
24	68	170	1.92	*	0.4667	14	30	0
25	87	172	2.06	5.5	0.5625	18	32	0
26	56	167	1.72	6.2	0.4375	14	32	0
27	67	172	1.88	4.6	0.4138	12	29	0
28	75	174	1.98	7.4	0.6176	21	34	0
29	72	*	*	6.8	0.5862	17	29	0
30	63	178	1.87	5	0.6875	22	32	1
31	68	174	1.91	7.8	0.6	18	30	0
32	72	182	2.06	*	0.4516	14	31	0
33	70	182	2.02	7.8	0.5484	17	31	1
34	68	168	1.84	5.7	0.5625	18	32	0
35	88	177	2.11	6.2	0.4857	17	35	0
36	75	174	1.99	5.4	0.5	17	34	0
37	83	172	2.04	5.7	0.625	20	32	0
38	74	170	1.92	*	0.5161	16	31	0
39	59	155	1.62	5.8	0.5172	15	29	1

* = missing data

APPENDIX B:

Ventricular Fibrillation induction technique:

That there is no single ideal technique for the induction of ventricular fibrillation to enable ICD testing is shown by the diversity of fibrillation induction functions on currently available devices (Table B.1). The induction of ventricular fibrillation induction at the time of ICD implantation is of particular importance and despite the availability of ramp pacing, programmed electrical stimulation, and the use of one or more AC fibrillators it has on some occasions proved impossible. The difficulty in inducing ventricular fibrillation in some patients and the observation that ventricular fibrillation was occasionally induced in these patients when a low energy cardioverting shock was applied to terminate ventricular tachycardia or flutter lead us to develop a new technique for inducing ventricular fibrillation. Essentially this involves the delivery of a pacing ramp which increases rapidly in rate over a period of 5-7 seconds until just below the rate at which exit block develops. At this point a 30 joule unsynchronised shock is delivered from an external defibrillator to the rescue defibrillation patches which are routinely applied to these patients. A pilot study of this technique was conducted in 12 patients. Sustained VF was successfully induced by this technique in all 12 patients (100%). In total 22 episodes of VF resulted from 41 attempts (54% success) at induction. Comparing successful with unsuccessful attempts to induce VF there was no difference between pacing cycle length (219 v. 220ms p=NS) or duration of pacing prior to external shock delivery (11.4 v. 11.3 seconds p=NS). No relationship existed between the success of fibrillation induction and the coupling interval of the 30 joule shock to the last pacing spike. The ECG of a successful fibrillation attempt using this technique is shown in figure B.1. This technique may be effective because it achieves dispersion of refractoriness through the ventricles by rapid pacing. This effectively results in prolongation

of the "vulnerable period" so that an external shock is capable of inducing ventricular fibrillation.

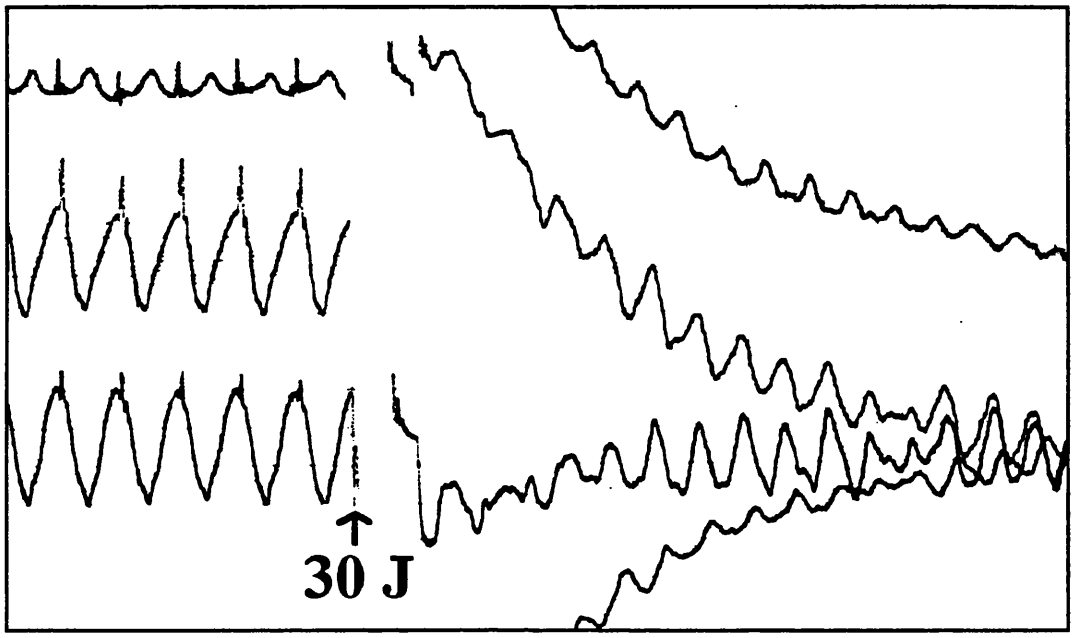

Figure B.1: Induction of ventricular fibrillation by delivery of an external 30J shock during rapid ventricular pacing. The disorganisation of the paced rhythm into ventricular fibrillation is seen immediately following the shock (30J)

Table B.1: Fibrillation induction devices in ICDs used in this study.

MANUFACTURER	CPI			MEDTRONIC	TELECTRONICS			VENTRITEX
MODEL	Ventak P Model 1600	Ventak PRx Model 1700	Ventak P2 Model 1625	PCD 7216A / 7217B	Guardian			Cadence
FIBRILLATION FACILITY					4202	4210	4204	
None	+				+			
VVT Pacing						+	+	
External triggered pacing via programmer		+						
PES facility				+				+
High frequency (20-30Hz) pacing			+					+

APPENDIX C:

Measurement Protocols:

Calculation of left ventricular ejection fraction from RAO 30° projection left ventricular angiogram.

Left ventricular ejection fraction was measured using a simple draw-round computer system and the following equations (Dodge *et al.* 1983):

$$\text{Left ventricular volume} = \frac{0.849 * A^2 * f^3}{L}$$

Where **A** is the area of the left ventricle on the RAO projection, **L** is the major axis of the ventricle in this projection and **f** is the magnification factor

When calculating the ejection fraction **f** cancels out and the equation becomes:

$$\text{Ejection Fraction \%} = 100 * \left(1 - \left(\frac{A_{sys}^2}{L_{sys}} \Big/ \frac{A_{dias}^2}{L_{dias}}\right)\right)$$

Where **sys** are the values in systole and **dias** are the values in diastole

Ventricular Stimulation protocol (Wellens *et al.* 1985)

Single and double extrastimuli during sinus rhythm

Single and double extrastimuli following 8-beat ventricular pacing drives at 600, 500, and 400ms.

** ** ** ** **

APPENDIX D:

Manufacturers and trademarked products referred to in this thesis:

CPI -	Cardiac Pacemakers Inc., St. Paul, MN 55112, USA
	Endotak
	Ventak
	PRx
Medtronic -	Medtronic Inc., Minneapolis, MN 55432, USA
	PCD
	Transvene
	NTL
Telectronics -	Telectronics Pty Ltd, Lane Cove, NSW 2066, Australia
	Guardian
	EnGuard
	DF
Ventritex -	Ventritex Inc., Sunnyvale, California 94086, USA
	Cadence

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