Defibrillation, the Coronary Venous System and the Passive Electrode Affect

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ABSTRACT

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DEFIBRILLATION, THE CORONARY VENOUS SYSTEM AND THE PASSIVE ELECTRODE AFFECT by John Robert Paisey

Introduction; implantable cardioverter defibrillators are becoming an increasingly accepted treatment for primary and secondary prevention of arrhythmic death. Key to the efficacy and future development of these devices is the defibrillation threshold (the amount of energy required to reliably terminate fibrillation). Changing the vectors of defibrillation through lead positioning has the potential to reduce defibrillation threshold. Current methods for the assessment of defibrillation threshold in humans lack repeatability and precision.

Methods: we undertook a program of human and porcine studies to investigate the impact on defibrillation threshold of placing electrodes in the coronary venous system. Both actively connected and passive (adjacent, unconnected) coronary venous electrodes were studied. We also developed and evaluated a method of assessing defibrillation threshold by delivering several test shocks following each induction.

Results: in defibrillation from the middle cardiac vein placement of a passive electrode affect reduces defibrillation threshold by 17%. Middle cardiac vein electrodes exert no passive electrode affect on right ventricular endocardial defibrillation. In the pig anodes comprised of middle cardiac vein alone are equally effective as tied middle cardiac vein, right ventricular anodes. Both these anodes decrease defibrillation threshold compared to right ventricle alone. The novel method of defibrillation threshold assessment developed increases repeatability compared to current algorithms. In human studies neither middle cardiac vein nor auxiliary lateral cardiac vein defibrillation decrease defibrillation threshold.

Conclusions: the passive electrode affect has the capacity to decrease defibrillation threshold. There is a discrepancy between the efficacy of coronary venous defibrillation in man and pigs due to the difference in orientation of pig and human hearts and the higher impedance of the configuration in man. A defibrillation threshold assessment algorithm delivering several test shocks after each induction may replace binary searches as gold standard in clinical studies.

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Abbreviations Used

A	Amp
AC	Alternating Current
ACC	American College of Cardiology
AHA	American Heart Association
ATP	Anti Tachycardia Pacing
CHF	Congestive Heart Failure
CI	Confidence Intervals (95% if not otherwise stated)
CRT	Cardiac Resynchronisation Therapy
CS	Coronary Sinus
CV	Cardiac Vein
DFT	Defibrillation Threshold
ED_x	Defibrillation $Efficacy_{percentage}$
EF	Ejection Fraction
IHD	Ischaemic Heart Disease
J	Joule
LCV	Lateral Cardiac Vein
LV	Left Ventricle
MCV	Middle Cardiac Vein
NASPE	North American Society of Pacing and Electrophysiology
post CV	Posterior Cardiac Vein
RV	Right Ventricle
s	Second
V	Volt
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
Ω	Ohms

1 INTRODUCTION

1.1 The History of Implantable Defibrillators

In the late 1960s when Dr Harry Heller died of a ventricular arrhythmia the implantable cardiac (or cardioverter) defibrillator was first conceived. His protégé, Dr Michael Mirowski, had witnessed Heller's hospital admissions with life threatening ventricular arrhythmias. At this time the concept that electricity was the best treatment for electrical problems was becoming accepted and use was made of the external defibrillator in hospitals whilst permanent pacemakers for the treatment of bradycardia were being refined(1). Mirowski's hypothesis was that individuals identified as at high risk of arrhythmic death might be protected by a pacemaker like device which once implanted could detect and terminate life threatening arrhythmias(2).

By 1969 through collaboration with Dr Morton Mower at Sinai Hospital, Baltimore USA, he had designed built and tested in dogs a prototype implantable cardioverter defibrillator (ICD)(3). Through the 1970s, supported by Medrad Inc of Pittsburgh USA, they developed their ideas through animal and human studies. Landmarks were the first chronically implanted device in dogs(4), and the acute human trials reported 1980(5). Publication of their concepts and results led to vitriolic derision although one future luminary of ICD research was to vigorously defend them(6). Much of the criticism centred on the difficulty of predicting which patients will benefit from the treatment, whilst the concept is now proven the patient selection debate rages as hotly now as it did then.(7-10) At the time of the proof of the implantable defibrillator concept anti-tachycardia pacing functions were being added to pacemakers with promising results(11;12), this capability was later to be the domain of ICDs(13;14). Then in December 1980 the first series of human implants at Johns Hopkins Hospital was reported leading, five years later, to the United States Food and Drug Administration (FDA) approving a device for clinical use(5).

Mirowski's original concept was of a transvenous implant but the size of the device (250g), problems with stability of electrodes and high defibrillation thresholds had led to early human devices being implanted at thoracotomy with epicardial patch electrodes. The commercial potential of the ICD was now widely appreciated by industry and well funded research allowed such improvements in size and stability that the first non-thoracotomy system (CPI, St Paul MN USA) was implanted in 1986(15) with competitors entering the market three years later(16).

The switch from thoracotomy to transvenous implants marked an increase in the acceptability of the device to patients and physicians and allowed an increase in implant rates that continues to this day(7;17;18).

1.2 Current Indications

The conflicting influence of proven efficacy and high cost of ICDs has made them subject of epidemiological and health economic scrutiny. Current indications fall into primary(19-21) and secondary(22-24) categories with a number of randomised controlled trials in each group.

The main secondary prevention trials compared pharmacotherapy (predominantly amiodarone) with ICD in survivors of life threatening ventricular arrhythmias. Meta-analysis of the ICD arm of three trials demonstrated a hazard ratio of 0.72 (CI 0.6-0.87) for mortality and 0.5 (CI 0.37-0.67) for arrhythmic death(25).

The primary prevention trials have targeted predominantly those with ischaemic heart disease and impaired left ventricular function. Initially these patients were further risk stratified by Holter monitoring and electrophysiological testing, finally reduction in mortality was demonstrated, hazard ratio 0.69 (95% CI 0.5-0.93), without the requirement for further risk stratification in the group with left ventricular ejection fractions (LVEF) under 0.3.

There are a further group of patients at high risk of arrhythmic death in whom, by consensus, ICDs are accepted primary prevention therapy but randomised trials have not been performed. These include cardiomyopathies(26;27), repolarisation abnormalities(28-31) and congenital structural heart disease(32).

Guidelines based on these principals have been formulated by responsible bodies and are used to guide clinical practice(26;28;33).

1.3 The Nature of Ventricular Fibrillation

Ventricular fibrillation has been defined as the chaotic, random, asynchronous electrical activity of the ventricles due to repetitive re-entrant excitation and/or rapid focal discharge(34). Whether it is truly chaotic has been challenged in recent years by the second clause referring to re-entry, a term which would not originally have been included in the definition. The classical dichotomy between tachycardia and fibrillation, long blurred by phenomena such as polymorphic tachycardia and ventricular flutter, is also becoming increasingly tenuous.

Fibrillation may be considered on several levels: ion channels, cellular action potentials, regional myocardium and the entire organ.

At the level of membrane based sodium, potassium and calcium channels ion flux is a basic requirement for depolarisation and restitution: instabilities in these processes may create the inconsistencies at higher structural levels that are a prerequisite for automacity and re-entry.

Cellular action potential characteristics, particularly restitution of conduction velocity and action potential duration, are widely believed to be crucial to the degeneration of more organised rhythms into fibrillation(35). Differential refractory periods lead to the phenomenon of wave breaks, key to the restitution hypothesis of fibrillation: as an

organised action potential sequence sweeps through myocardium refractory cells encountered have the potential to break the wave front.

At the regional myocardial level structural (e.g. physiological connective tissue or scar) and functional (e.g. ischaemic, injured or metabolically deranged tissue) barriers create areas of differential restitution(36). As a tachycardia front (mother rotor) sweeps through wave breaks at these points generate eddies of re-entry (daughter rotors) that given the right substrate may propagate generating fibrillation(37).

At the level of the heart as an electrically conducting organ the sick ventricle is prone to a slippery slope: the disease processes leading to re-entry and abnormal automacity generate slowly propagated impulses. The same disease processes also generate differential restitution facilitating the further decline of the rhythm, figure 1.1↵. At this level circumstances exist in which wave breaks may be generated without the prerequisite of a mother rotor. Action potential duration restitution is a dynamic property dependant on cycle length, if the slope of action potential duration versus cycle length is steep (>1) even an apparently benign variation in rate may generate a positive feedback phenomena resulting in increasing restitution heterogeneity (detected in the whole heart as electrical alternans) and then fibrillation(38). This sequence is now recognised to be an example of the influence of chaos theory principals on a biological system(35).

1.4 Concepts of Defibrillation

Defibrillation may be defined as the arrest of fibrillation of the cardiac muscle (atrial or ventricular) with restoration of the normal rhythm(39). Cardioversion is the restoration of the heart's rhythm to normal by electrical countershock(39). The fundamental process at the ion channel/cellular level is electroporation(40).

There have been three coherent attempts to describe the process of defibrillation and its' success or failure,

(i) the total extinction hypothesis(41)

(ii) the critical mass theory(42) and

(iii) the upper limit of vulnerability theory(43).

The total extinction hypothesis This was the first attempt to explain defibrillation and stated that fibrillation consisted of multiple wave fronts at varying states of polarisation: in order to terminate fibrillation sufficient energy should be delivered to depolarise the entire ventricular myocardium thus terminating all wave fronts and allowing restoration of normal rhythm. It was based not on experimental data but a concept of VF and is therefore hypothesis as opposed to theory.

The critical mass theory In order to explain how a discharge of energy restores the heart to its resting rhythm a hypothesis was formed that electrical activity must be terminated in a certain proportion of myocardium (a critical mass) in order to restore underlying rhythm.

The hypothesis was explored in dogs by attempting to terminate VF by injecting potassium chloride into various combinations of coronary arteries. The greater the proportion of myocardium included in arteries selected the greater the probability of terminating VF. It was observed that therapies that left appreciable areas of myocardium outside the territory targeted there remained a significant chance VF would be terminated.

The conclusion drawn by the authors was that it was not necessary to depolarise all myocardium but the probability of successful termination of VF was dependant on the mass of myocardium depolarised. The defibrillation threshold (DFT) could be regarded as a measure of success in depolarising a critical mass of myocardium.

The weakness of the experimental method underpinning this theory is the assumption that mechanisms of chemical and electrical defibrillation are analogous.

The upper limit of vulnerability by measurement of intra-cardiac electrograms during failed defibrillation it was observed that at energy deliveries above 1 J all wave-fronts are

terminated but after an interval fibrillation re-initiates(44). This contradicted both the total extinction and critical mass theory as it demonstrated that terminating all fibrillation wavelets is not necessarily sufficient to defibrillate successfully. The key to understanding why this should be is the appreciation that defibrillation involves not just terminating fibrillation but also preventing its' re-initiation. Because fibrillation is a chaotic process myocardium is at differing states of refraction, energy dose should be sufficient to terminate all wave fronts and render myocardium incapable of re-initiating fibrillation before the next synchronized contraction.

Further evidence supporting this theory was obtained from the correlation between DFT and the upper limit of vulnerability. The upper limit of vulnerability is the threshold above which VF is not initiated by a T wave shock: energy applications synchronised with T waves have three distinct phases, below a given level VF is not induced, above this but below a second threshold VF is induced, finally above the second threshold VF is not induced. The second threshold is the upper limit of vulnerability(43).

This observation gave the explanation of defibrillation mechanism its' name. The proposed explanation being that above the upper limit of vulnerability, fibrillation is not induced for the same reason that it is terminated in defibrillation: myocardium is rendered refractory until the next coordinated contraction.

The critical mass theory needs to be rethought rather than rejected in the light of these findings. Einstein's general relativity may be a more complete explanation than Newton's Principia Mathematica but the laws of motion still provide a useful way of predicting events on a human scale. Similarly the principal message of the critical mass theory (that energy distribution is an important variable) should not be rejected. It may be that if the critical mass in question were the proportion of myocardium rendered refractory rather than depolarised the theory would become accurate.

1.5 Defibrillation Threshold

There is no universally accepted definition for DFT but it is generally used to indicate an energy level at which defibrillation is unlikely to fail(45-47).

Defibrillation has an intrinsic probabilistic nature, at any one energy level a number of shocks will succeed and a number will fail. It is only at the extremes that 100% will fail or 100% will succeed, figure 1.2↵. The most precise assessment of DFT requires the administration of hundreds of inductions and defibrillation attempts to an excised whole heart preparation. For this a beating animal heart is explanted, isolated and perfused in a nutrient solution(48). With the number of therapies that may be delivered in this preparation the probability of success of each configuration at each energy level may be determined. The sigmoid nature of the probability of success and a precise value of the ED*x* (energy level at which *x*% of therapies will be successful) is described(49). For any given energy the probability of success can be determined. For example the energy that will give a 50% probability of successful defibrillation is denoted as the ED_{50}.

The major disadvantage of such preparations is the lack of equivalence to an in vivo defibrillation, the influence of extra-cardiac tissue is lost and the impact of duration of arrhythmia is muted by continuing metabolic substrate supplied to the myocardium.

Excised whole heart preparation experiments do give insight into the importance of entering the final step up/down pathway at an appropriate point. Entering the pathway below or above the DFT drags the final result in the direction of the entry point due to the probabilistic nature of each outcome(50).

It is impossible in the clinical or experimental laboratory to plot a dose-response curve for each electrode configuration as this would require an unacceptably large number of shocks. In an animal study although such large numbers of shocks are prohibitive defibrillation threshold is still determined using multiple fibrillation/defibrillation cycles. The energy of the defibrillation shock is then increased/decreased depending on

failure/success. Whilst it would be ideal to determine a point towards the upper flat portion of the curve (E_{99}) it is generally found that the defibrillation threshold is measured at a point on the slope of the curve. The starting point of the protocol may determine the position of the defibrillation threshold on the curve. If a high starting energy is selected with progressive decrements in energy (*step-down protocol*) defibrillation thresholds are generally distributed asymmetrically towards the upper end of the dose response curve with the average location at the E_{71} (range E_{25} to E_{100})(50). Starting at a low energy and incrementing (*step-up protocol)* produces a distribution of DFTs at the lower 3/4 of the curve, skewed towards the lower end. If a level in the middle range is selected as a starting point (*mid-point protocol*) the DFTs tend to be in the upper 3/4 of the curve but the distribution is centred towards the middle of the curve, figure 1.3↵.

Once the defibrillation threshold has been established using one of these three methods it has been proposed that if further fibrillation/defibrillation cycles are performed at this level then a higher degree of certainty can be made that the defibrillation threshold is located at the upper end of the curve. Therefore if the defibrillation threshold is found to be at *x* joules and then this succeeds twice more then the worse case scenario is that the defibrillation threshold lies at E_{75}. Using estimated probability functions from animals and humans three methods of defibrillation threshold determination have been compared(51). (i) stepping down to the first failure; (ii) stepping up to the first success; and (iii) doing both 1 and 2 and averaging. The third method had the lowest total error. Three methods of determining the E_{50} for a given electrode configuration were examined(52). The first involved starting at a level approximate to the E_{50} and then incrementing/decrementing depending on failure/success by 1 joule each time. When three reversals had been obtained the protocol was stopped and the E_{50} determined to be the mean of the three energies at reversal. The second method used a similar up/down protocol but continued for 15 shocks and also reduced the size of the increment/decrement by 20% of the preceding shock. In

the final estimation 5 shocks were delivered at 5 energy levels in 2-joule increments. A probability of success curve was plotted using linear regression and the E_{50} calculated. It was found that the latter technique produced a slightly higher result than the other two. It was concluded that there was not a vast difference between the techniques, with the first two requiring fewer fibrillation/defibrillation cycles than the third.

In animal studies these principals have been applied and a three or four reversal binary search is undertaken. The point of entry onto a final pathway is determined by a step up/step down algorithm as described above. A further step up/step down search is then undertaken with the increments as small as the programming of the defibrillator allows. After the preordained number of reversals has occurred the DFT is taken from the successful attempts prior to each reversal. Such a protocol generally involves 10-15 inductions and defibrillation attempts per protocol, (53-55) an example of such a protocol in use is shown, figure 1.4↵.

If a clinical trial is to be undertaken and a comparison made between configurations or individuals an approximation of the DFT is obtained by performing a limited step up/step down binary search(56). Due to the potential harmful results of multiple episodes of VF and defibrillation attempts the number of inductions and therapies delivered is normally restricted to six in an individual. If two configurations were to be considered in an individual this would allow only three inductions and defibrillation attempts per configuration giving only a very approximate DFT(57).

A frequently employed method in the clinical practice is the verification technique. In this an energy level is taken which is usually 10 or more joules less than the ICDs maximum output and the success rate is measured over 1 to 3 shocks. If successive defibrillation attempts are successful this is accepted as the DFT(58). If not then the system is usually revised. This value would be better described as the safety margin as it assesses only likelihood of success (not failure). It is generally thought to be E_{99}, however, when

measuring the defibrillation threshold, it is apparent that this is frequently at a level less than E_{99}. This technique is not accurate enough to be able to compare two or more electrode configurations.

1.6 Determinants of Defibrillation Threshold

DFT is influenced by both the substrate and the system. Known substrate factors include body weight, left ventricular dimensions, certain drugs and time since initiation of arrhythmia(59-61). System factors such as lead dimensions, shocking vector and waveform are implicated(62-66).

Body weight and ventricular dimension a high body weight(62) and increased left ventricular dimensions(59;67) are shown to be associated with high DFT in humans and a correlation exists between DFT and body weight in pigs(68). It is not known whether the impact of body weight is solely an association with increasing left ventricular dimensions or if the influence of non-cardiac tissue is a factor.

Pharmacological affects it is widely appreciated that amiodarone increases DFT(61;69-71) and most implanting centres will perform a defibrillation efficacy check if an existing defibrillator patient is started on the drug(70;72). It has been suggested that propafenone may decrease DFT although this not recognised as a clinical issue(73). The likely mechanism of these effects is on membrane stability through their affect on ion channels. In the case of propafenone sodium channel blockade may make re-induction of VF after a defibrillation attempt less likely, the range of amiodarone's action are so wide that it is speculative to consider which of the actions or combination of actions is responsible(74).

Duration of arrhythmia it is generally accepted that DFT increases with duration of VF(75) and one study has suggested DFT more than doubles between 2 and 10 seconds of VF duration(60). It is postulated that this is due to increasing fibrillatory wavelets(76),

increased sympathetic output(77;78;79) and ventricular dilatation(80). There is some suggestion that the DFT falls after this peak with second defibrillation attempts at the same energy level having a higher success rate than first attempts(81). As time increases further DFT increases again due at least in part to the effect of chronic myocardial ischaemia(82), derangements in acid base and biochemical homeostasis may also alter DFT(83;84).

Electrode dimensions electrode shape is an important factor in DFT. A high surface area of electrode reduces DFT mostly by reducing impedance. This will influence DFT measured by energy more than by current(85).

The area of contact between electrode and myocardium is a further factor(86). In one study of epicardial patch electrodes the size of the patch impacted on the DFT but the position of the patch did not(65). This contrasts with endocardial electrodes where position is known to be an influential factor(87).

The available evidence suggests that for efficient defibrillation an electrode should have the largest possible surface area and as much of this surface as possible should be in contact with myocardium. It is probable though not proven that spreading this surface area adds further benefit, a mesh electrode should be superior to a plate electrode for the same surface area.

Electrode position the position of the electrodes in relation to the heart impacts on DFT by controlling the apparent shocking vector. Current takes the route of least resistance, not the shortest route, from distal to proximal electrodes but presenting a direct pathway involving the maximum mass of myocardium decreases the impedance of the route involving this myocardium, extrapolating from the critical mass theory DFT should be minimised.

Multiple animal and human trials been conducted to deduce the optimal polarity. Recent trials with current technology have shown designating the distal electrode as anode results in the lowest DFT(81). There is still conflicting evidence on the value of reversing the

polarity if initial DFT testing fails to establish a safety margin(81;88;89). It is common clinical practice to program devices to reverse the polarity of defibrillation after a number of failed attempts.

It has been shown that involving the septum in shocking vectors reduces DFT(90) and in right ventricular endocardial electrodes a proximal position is inferior to an apical position(87).

Manoeuvres such as introducing additional electrodes (transvenous, epicardial or subcutaneous) both increase the surface area of the composite electrode and manipulate the shocking vector.

Defibrillation waveform developments in energy waveform delivery contributed to a reduction in DFT. Parameters that have been addressed include: polarity, phases, pulse width and tilt.

Waveforms have evolved from monophasic rectangular to biphasic decaying morphologies(91). Towards the end of the epicardial patch era it became appreciated that biphasic waveforms permit effective defibrillation at a lower total energy delivery than their monophasic counterparts. More work on biphasic waveforms was undertaken with transvenous electrodes and this finding has been confirmed several times over(63;64;92). The initial explanation given was that it is rapid change in polarity from positive to negative (or vice versa) that is the effective defibrillation mechanism. This was challenged by the findings that a delay between phases does not inhibit defibrillation and that decaying the first phase exponentially improves efficacy despite reducing the peak to trough polarity change(92-94). The alternative explanation forwarded was that first phase imparts charge to myocytes not rendered refractory and that these become triggers for re-induction of fibrillation. Inserting an inverse polarity phase removes the charge from these myocytes, a process that requires less energy than defibrillating the cells in question.

Triphasic waveforms have also been studied but have proved inferior to biphasic morphologies(95).

Contemporary understanding of what constitutes an optimal waveform form consists of: a high leading edge energy/total energy ratio with distal electrode as anode for the first phase followed by an exponential decay to 60% of energy dissipation and a second phase of reverse polarity discharging the remaining 40% of total energy. This is achieved by having relatively small capacitors, which give the added benefit of reducing charge times and thereby detection to therapy interval(96).

As previously alluded to DFT is usually measured by energy and in clinical systems this is the most logical variable to examine as it will determine charge times and battery life. It is however current, not energy, that is responsible for defibrillation and in certain circumstances it should be this that is examined, furthermore only DFT by current is independent of impedance(97).

1.7 Coronary Venous Defibrillation

Interest in coronary venous defibrillation began as the change was made from epicardial patch electrodes to intra cardiac coils. Intra cardiac coils have the advantage of being implantable transvenously reducing procedure duration and complications compared to the thoracotomy required for epicardial electrodes(98). The trade off was a rise in DFT(99). This was unsurprising, compared to patches coils have a smaller surface area, a smaller area of myocardial contact and their position creates an apparent shocking vector involving less myocardium.

In the quest for an electrode position combining the implantation benefits of coils with the positional benefits of patches the only practical candidate is the coronary venous system. It is epicardial, provides access to most parts of the heart surface and is used for

the deployment of pacing electrodes. The various published studies on the coronary venous defibrillation are summarised in figure 1-5.

Animal studies have assessed main coronary sinus, great cardiac vein, middle cardiac vein and lateral cardiac vein as sites for epicardial lead placement(55;100-103). These have been combined with a conventional epicardial RV electrode and used as single site electrodes.

Human studies have examined auxiliary defibrillation from MCV(103) and LCV(101;102). The hypotheses between these two sites are subtly different. The LCV assumes the low current density in LV free wall reduces efficiency of defibrillation and investigators targeted the area with a separate capacitance low energy auxiliary defibrillation. The MCV investigators assumed that MCV was an intrinsically superior route of defibrillation and allowed a single capacitance defibrillation with RV and MCV as alternatives. The LCV offers the advantage of being an attractive site for resynchronisation pacing, the MCV the advantage of potentially replacing rather than augmenting the RV endocardial coil.

1.8 The Passive Electrode Affect

In discussing the passive electrode affect it is first necessary to define the terms used. For the purposes of this thesis I will be using the following definitions.

Bystander electrode: an electrically conducting structure that approximates with but is not connected to a defibrillation or pacing circuit.

Passive electrode: a bystander electrode that alters electrical characteristics of a circuit.

Passive electrode affect: the influence of a passive electrode on circuit characteristics. A passive electrode affect might exist on impedance, current distribution or DFT and may increase or decrease these parameters.

Inactive electrode: a bystander electrode that exerts no passive electrode affect.

Virtual electrode: a biological structure, usually myocardium, which functions as an electrode when subjected to an electrical pulse. Defibrillation would require extremely high energy were it no for this phenomenon altering the otherwise exponential decrease in current density with distance from source.

Phantom electrode: this term is ambiguous having been used for both virtual and passive electrodes: I will avoid it.

There are three animal studies that have examined the passive electrode affect. Two studies were concerned with the impact of bystander epicardial patches on endocardial defibrillation.

In the first of these(104) the impact of conductive and non-conductive epicardial patches on the antero-lateral aspect of pericardium were examined in a dog model. DFT was determined from RV to SVC coils without an epicardial patch, with a conductive patch and with a nonconductive patch. The conductive patch increased energy required for defibrillation by a factor of 2.1 and reduced by 72% the potential gradient in myocardium under the patch. In contrast the nonconductive patch did not alter DFT or potential gradient compared to control.

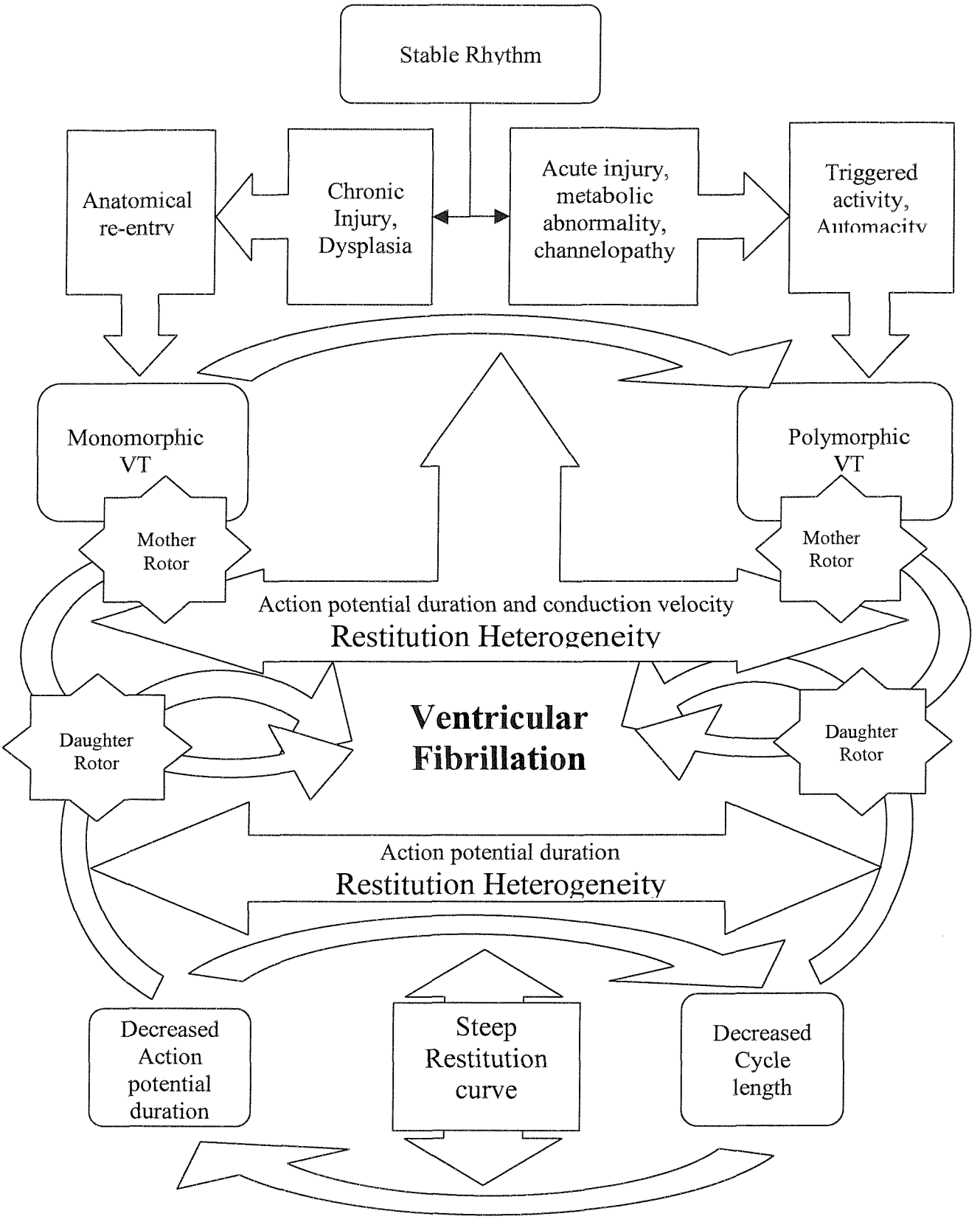
The other study(99), also on dogs, examined various combinations of left and right ventricular epicardial patches as well as a subcutaneous array on DFT. It was found that when defibrillating from an RV endocardial electrode the DFT was increased by the presence of bystander LV and RV epicardial patches whether the cathode employed was SVC, SVC and subcutaneous array or sub pectoral plate. A similar affect was observed with LV only but not RV only epicardial patches. In contrast, incorporating the epicardial patch electrodes into the defibrillation configuration reduced the DFT.

The canine model was also used to assess the influence of bystander endocardial pacing and defibrillation electrodes(87)on endocardial defibrillation circuits. It was found that, even if the bystander and active lead were in contact, no difference in DFT was observed.

There was a small but significant decrease in impedance when contact was made between active and bystander defibrillation coils. Foregoing an apical position of the active electrode to avoid proximity with a bystander coil produced an increase in DFT.

The conclusion drawn by the authors was that no passive electrode affect on DFT is seen with endocardial bystander electrodes but clinicians may see an increase in DFT if they compromise lead position.

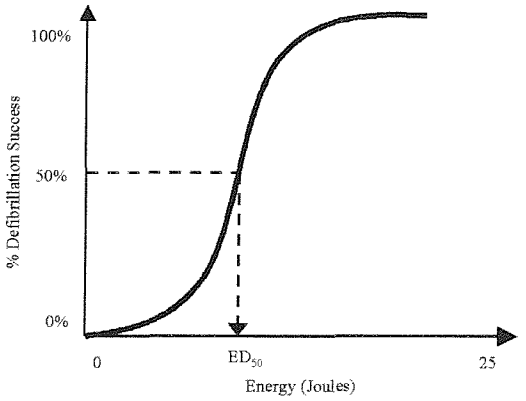
Figure 1-1 Role of Restitution in the Development of Ventricular Fibrillation



Positive feedback mechanisms in VF generation.

↵

Figure 1-2: Probability of Success Curve.



Typical dose-response curve for ventricular defibrillation. ED_{50} represents the energy level that achieves 50% successful defibrillation.

↵

Figure 1-3 Comparison of Different Threshold Measurement Methods.

Comparison of possible positions of the defibrillation threshold on the dose-response curves using three different methods. Incr = step-up method, decr = step-down method, midpoint = step-up or down depending on result, but starting at a point predicted to be near to the defibrillation threshold.

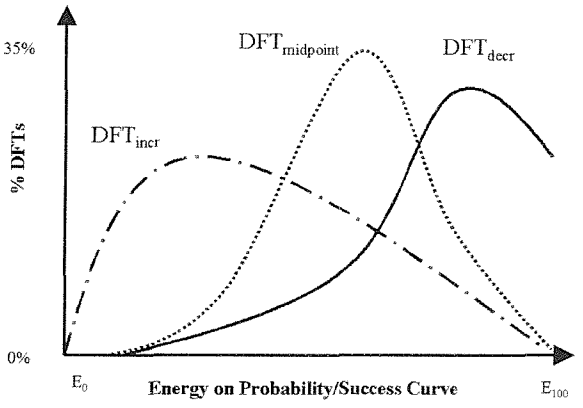


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Figure 1-4 A Binary Search Algorithm in Use

Test shock	Strength (J)	Outcome	Action
1	16	Failure	Step up to 22 J
2	22	Success	Step down to 18 J
3	18	Success	Enter final DFT determination pathway on downward trajectory 1 increment below
4	16	Success	Step down 1 increment
5	15	Failure	First reversal- step up one increment
6	16	Failure	Step up 1 increment
7	18	Failure	Step up 1 increment
8	20	Success	Second reversal, 20 J contributes to DFT
9	18	Success	Step down 1 increment
10	16	Success	Step down 1 increment
11	15	Failure	Third Reversal , previous success (16 J) averaged with previous point (20 J) to yield DFT of 18 J

Figure 1-5 Published Studies of Coronary Venous Defibrillation

Study	Model	Configuration (Control in italics)	Additional detail	Main Findings
Bardy et al 1990(100)	Man	*RV→Thoracic patch* RV→Coronary sinus	Superseded by active can and SVC coils	Coronary sinus superior to thoracic patch cathodes
Roberts et al 1999(53)	Pig	*RV→AH* RV+MCV→AH MCV→AH	High impedance MCV electrode	RV+MCV superior to RV alone
Roberts et al 2000(54)	Pig	*RV→AH* RV→SCV+AH RV+MCV→AH MCV→AH	Multifilamented MCV Electrode	Both MCV configurations superior to both both non MCV configurations
Roberts et al 2000(55)	Pig	*RV→AH* RV+MCV→AH	MCV auxiliary shock preceding RV→Can	Auxiliary shock superior
KenKnight et al 2000(105)	Dog	*RV→SVC* RV+ post CV→SVC	post CV auxiliary shock preceding RV→SVC	Best result with shortest intershock interval
Roberts et al 2001(106)	Pig	RV+MCV→SVC+AH, RV+MCV→AH	Varying primary and auxiliary shocks RV vs MCV	Auxiliary shock in MCV superior for both cathodes
Walker et al 2001(107)	Pig	post CV+RV→SVC	Auxiliary shock strength and timing varied	Any auxiliary shock strength before or simultaneous to main shock effective
Meisel et al 2001(102)	Man	*RV→SVC+AH* RV+CV→SVC+AH,	A pilot study testing various CV sites	Trend to reduce DFT with auxiliary shocks in lateral cardiac vein
Butter et al 2002(101)	Man	*RV→SVC+AH* RV+lat CV→SVC+AH	Separate capacitor for auxiliary shock	Auxiliary shock reduced DFT significantly
Roberts et al 2003(103)	Man	*RV→SVC+AH* RV+MCV→AH	Number of electrodes maintained constant	No difference in DFT by energy, impedance higher in MCV, DFT by current lower in MCV

2 EXPERIMENTAL METHODS

The principals guiding the methods for the animal and human defibrillation studies are discussed in this section. Specific protocols are given in the relevant chapters and the methods of the epidemiological study are given in that chapter.

2.1 Animal Studies Methodology

2.1.1 Ethical Considerations

The project was licensed by the British Home Office, myself, John Morgan and Paul Roberts are all personal license holders. Animal work was undertaken only after consideration had been given to the principals of replacement, reduction and refinement. No animal study was undertaken when the same information could be ethically obtained from a clinical study, or when an in vitro model could be used.

Multiple fibrillation/defibrillation cycles are required to evaluate different modalities of defibrillation, many studies cannot therefore be ethically performed on human subjects and tank studies do not reflect the interaction of cardiac and extra-cardiac tissue in defibrillation. While differences exist between animal and human anatomy and physiology, animal studies remain the only method of comparing accurate defibrillation parameters between configurations.

The maximum number of protocols possible was performed on each animal with a view to reducing the number of animals used. Statistical calculations were made to determine the fewest animals needed in each protocol to give a risk of type 2 error of 0.2 with risk of type 1 error of 0.05.

2.1.2 Choice of model

Considerations: The majority of large mammal defibrillation studies have been undertaken on pigs or dogs, a smaller number have used calves or sheep.

In selecting an animal model, it should ideally have the following properties: anatomical consistency, comparative physical size and anatomy, functional similarities of the myocardium and coronary circulation, similar cardiovascular disease pathogenesis to humans.

Anatomy: Anatomically the pig is the closest model to the human heart. The coronary circulation is almost identical and the size and shape of the swine cardiovascular system is very similar to that in humans although there are some differences in the pathways of ventricular excitation and distribution of the Purkinje fibres. Dogs are more similar to humans in the latter respect(108).

The dog has a larger heart weight/body weight ratio than the pig. The latter is more comparable to the human. The relatively large weight of the canine heart is likely to be due to the increased exposure of the dog to physical exercise compared to both the human and pig. It has also been shown that there is a much higher incidence of ventricular fibrillation in the pig than the dog after partial or total coronary occlusion. This may be because there are more inter-coronary anastomoses in the dog heart. The increased collateral circulation in the dog is again felt to be as a result of the relative high level of physical exercise. The coronary circulation of the pig is very similar to the human, whereas the canine differs considerably, in particular the left coronary artery(109).

Electrophysiology: In the first systematic attempt to identify a model for defibrillation research the species studied were dogs, calves, ponies and pigs. They used a defibrillation system consisting of two epicardial patches positioned at thoracotomy. The first patch was sutured to the apex of the left ventricle and the second to the base of the right ventricle. In some species they investigated differing sized patches. Ventricular fibrillation was induced with 60-Hz alternating current for 1 second. A rectangular 4-msec defibrillation pulse was delivered 10-15 seconds after VF induction. They calculated probability of success at a

variety of differing energy levels in each species. If a first shock failed they would deliver up to 3 shocks in total at the same energy level before delivering a rescue shock.

The level of success ranged from 44% with 6-joule shocks to 93% with 16-joule shocks. In calves the surface area of the patches was scaled up compared to the dog using body-weight scaling. The mean weight of the dogs was 25kg compared to 107kg of the calves. The probability of success was considerably lower for the calves when compared to the dogs. A series of 3 ponies (mean weight 99kg) was largely unsuccessful with only a total of four fibrillation-defibrillation episodes with the animals all ultimately dying prematurely. Defibrillation in pigs (mean weight 89kg) was more successful than the results in calves. However, with the pig study probability of success was measured at only one energy level with two patch sizes, making it difficult to compare with the dog where a more complete probability-success curve was plotted. They concluded that the studies in calves/ponies demonstrated defibrillation success rates as being at best moderate when comparing them to the dog. They also noted that using body-weight-scaled electrodes may have had an impact on success rate when comparing dogs to pigs, because of the discrepancy between the heart-to-body-weight ratios (pigs=0.005 and dogs=0.0082). They also concluded that large (i.e. >100kg) animals were probably unsuitable for defibrillation research(110).

One of the most significant electrophysiological properties that vary between species is the ventricular fibrillation cycle length. In humans it is approximately 200 msec. The following are reported cycle lengths of fibrillation in a number of animals(111):

Dog – 101 msec

Pig – 95 msec

Sheep – 110 msec

Isolated rabbit heart – 100 msec (Singer, 1993).

Human and swine electrocardiograms during ventricular fibrillation show a number of significant differences during VF over a period of 10 minutes(112). Human data was collected from patients who had VF arrests whilst carrying Holter monitors. The first obvious difference is the overall frequency which is higher in the pig. The initial frequency in the human was 4.23 ± 0.93 Hz compared to 13.7 ± 1.79 Hz in the pig. The patterns of change in the frequency varied between species with the human demonstrating two discrete peaks to the frequency at 55 seconds and 5 min 45 seconds before declining to approach 3 Hz at 10 minutes of VF. The pig, however, showed a decline from the initial frequency to a trough at 1 min 22 s before peaking at 3 min 55 s and then declining to a constant non-zero value. These are illustrated in figures 2.1↵ and 2.2↵ *(modified from Martin, Brown and Dzwonczyk, 1991).*

The dog's intrinsic electrophysiological/pacing parameters are markedly different from humans(113). In particular the R-wave and P-wave amplitudes are up to four times larger in the dog compared to the human. In the referenced study they recorded intrinsic and pacing parameters of a series of pigs and compared them to figures reported in the literature for both canines and humans, figure 2.3↵.

Probably the most significant findings were that the peak-to-peak amplitudes of the endocardial R-wave for the pig (5.9-10.4 mV) and man (6.9-17.9 mV) are similar, but both are much smaller than those of the dog (24.0-30.0 mV).

Hemodynamic: The normal hemodynamic parameters of the awake pig are comparable to normal human values(108). Figure 2.4↵ illustrates this point.

Biochemistry & Haematology: Data for man and pig are compared in figure 2.5↵.

Practical Considerations: With a "short list" of dog and pig as models for the animal experiments two important factors came into play. First, the Home office confers special status on dogs, cats and horses - below primates but above other large mammals. This status requires dogs only to be used where there is a clear advantage over farm animals.

This requirement is non-evidence based as pigs are at least as intelligent as dogs, it is however a legal specification. Second, there was a pre existent expertise on the part of medical (John Morgan and Paul Roberts) and technical (Kerry Taylor and Jas Barley) staff in porcine studies.

Animal Breed: there is no clear indication in the literature of cardiovascular or haematological differences between individual breeds of pig. One study identified differences in heart/body weight ratio from Hormel miniature pigs to the domestic pig(109). Animal defibrillation studies in the literature usually report only the species and not the individual breed. Animals used in these studies were selected on the basis of availability, they were of mixed breed with a large proportion of middle white heritage.

Choice of Model-Conclusion: The pig is a widely studied, conveniently sized, readily available species that the Home office approves and co-workers and supervisors have expertise in handling. It is the best choice for defibrillation studies in the time and place the experiments of this thesis were performed.

2.1.3 Animal preparation

Animal Care: all animals were transported to the research facility a minimum of 5 days before the scheduled procedure. When pigs are relocated their behaviour suggests anxiety. It was therefore felt that it was important for the animals to be comfortable and relaxed to avoid any base line sympathetic drive prior to starting each study. This also allowed time for them to be transferred to a new feeding regime and be treated for any infections or infestations.

Premedication: the animals were fasted for a minimum of six hours prior to induction of anaesthesia. The pigs were sedated with an intramuscular (neck) injection of Streznil (10mg). They were left for 15-45 minutes and the effects of the sedative were assessed. When the animal was adequately sedated a 22G butterfly needle was inserted into an ear

vein and 0.2mL/Kg of Saffan injected to induce anaesthesia. The animal was then transported to the operating theatre and a 22G cannula inserted in an ear vein.

Intubation and Ventilation: the pharynx was anaesthetised with local xylocaine (10mg in 40ml) spray and then intubated with a cuffed endotracheal tube, in the left lateral position. Intubation of the pig is not as straightforward as humans who have relatively straight upper oropharyngeal passages, the major difficulty in visualisation of the vocal cords is that the epiglottis lies in the oesophagus. A blunt ended metal trochar in the tube reduced the curve and enabled easier passage through the vocal cords. The trochar was then removed and the cuff of the tube inflated with air. The tube was secured to the animal with Elastoplast and connected to the ventilator. A CapeWain Multipurpose ventilator (Cape, Warwickshire, UK) was used with an open anaesthetic circuit using room air with supplemented oxygen (2L/min).

The technique of swine intubation is demonstrated figure 2.6↵.

Anaesthetic Preparation: Dr Paul Roberts and Dr David Smith who have previous experience of porcine anaesthesia had previously refined the anaesthetic protocol. Having initially used an intravenous Saffan they had found inhalational isoflurane gave better cardiovascular stability and was more practical. A closed circuit anaesthetic preparation was adopted with soda lime used to absorb excess carbon dioxide. Initially 5% isoflurane was delivered via an oxygen flow rate of 3L/min this was reduced to 2L/min once anaesthesia was established for the remainder of the procedure, depending on each animal's response.

Monitoring: a surface electrocardiogram (lead II) was continuously monitored throughout the course of all studies. Arterial blood pressure monitoring was performed via a percutaneous femoral artery puncture and use of the Seldinger technique to place an angiographic one-way valve sheath. I found this method preferable to cut down to a superficial femoral artery and cannulation with a venflon due to a more stable signal. Both

the ECG and blood pressure were displayed on the Hewlett Packard HP 78353B (Hewlett Packard, CA, USA) monitor.

2.1.4 Monitoring Induction and Defibrillation

Pulse generator: Inductions and defibrillations were delivered by an external replica of an implantable model (Medtronic 5358) unless otherwise stated. This was connected to a junction box (Medtronic 5421) and the defibrillation electrodes attached through this. The device delivers monophasic or biphasic impulses, biphasic was selected for all studies. It is also capable of delivering a range of VF inductions including 50 Hz AC current and shock synchronised T wave shocks. Defibrillation therapies are programmable at 0.2 J intervals from 0.4-2 J, 1 J intervals from 2-16 J and 2 J intervals from 16-34 J.

For two protocols a more modern device became available (Medtronic 7274) and was utilised. The waveform is identical but the device has the advantage of much shorter charge times, relevant in a study with VF time as an endpoint. The disadvantage of the device was its' non-rechargeable nature limiting the number of defibrillation attempts, and hence studies, per device. The device delivers the same range of inductions and defibrillation options with the exception of an upper limit of 30 J.

Fibrillation Induction: a number of electrical methods of induction of ventricular fibrillation have been reported in the literature. With early ICDs which required a thoracotomy and epicardial patches, 60Hz current was applied directly to the exposed ventricles. With the advent of the transvenous electrodes methods have changed to utilise the energy sources and circuitry within the device. Device-based methods to induce VF have included rapid burst pacing(114) and the delivery of low-energy shocks synchronised to the T wave(115). External shocks synchronised to the T wave have also been shown to be a reliable method of VF induction at the time of ICD implantation(116). External unsynchronised shocks delivered during rapid ventricular pacing have been reported to induce VF in patients when burst pacing from the device fails(117).

During rapid ventricular pacing and 50Hz alternating current induction there will be no cardiac output, which will prolong the ischaemic time. However induction of VF with synchronised T-wave shocks is less reliable. I therefore elected to use five second bursts of 50 Hz ac inductions repeated at 20 s intervals to induce VF.

Defibrillation Waveform: All currently available ICDs use a biphasic waveform to cardiovert ventricular fibrillation to sinus rhythm. In all of the experimental protocols a biphasic waveform has been used to mimic current clinical scenarios as closely as possible. ICDs deliver a tilted waveform with a capacitive discharged exponential decay with the second phase of the waveform usually being shorter than the first. In order to take into account individual patient and system characteristics the ICD modifies the waveform depending on the impedance of the last delivered shock. This ensures that the correct energy is actually delivered to the patient as near as possible. The manner in which the waveform is altered varies from device to device. Some alter the tilt of the waveform (keeping the duration constant) whereas others alter the duration of the first phase (keeping the tilt constant) i.e. increasing the length of the first phase will result in more energy delivered overall. However, in an experimental protocol investigating defibrillation pathways it is desirable to have as few variables as possible. It is highly likely that the shock impedance of one pathway will differ from another because of differing tissues being incorporated within the different electric field generated. It may be argued that rectangular waveforms are preferable in the research situation as they allow administration of a known total energy whereas tilted waveforms deliver an approximate energy dependant on the electrical properties. Clinically used pulse generators however universally deliver tilted waveforms making such impulses closer to the norm.

We elected to use a device delivering a biphasic exponentially decaying waveform to mimic the clinical situation but record the delivered as well as programmed energy to confirm consistency.

2.1.5 The Defibrillation Threshold

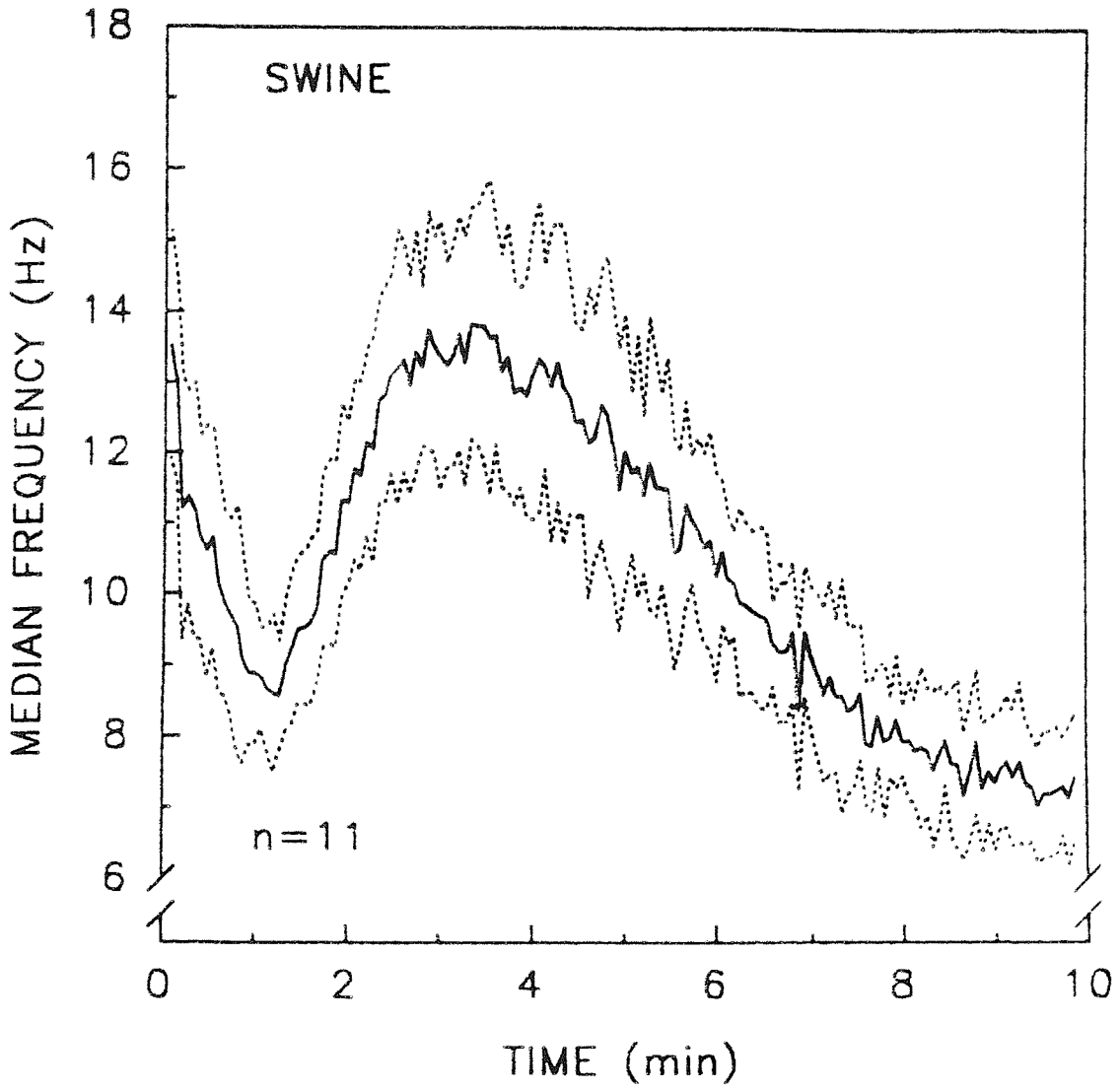
In studies described in this thesis a number of different defibrillation pathways are to be compared with one another. To make this comparison it is necessary to have an endpoint. It is usual to describe this in terms of energy requirements in the form of joules. The defibrillation threshold is generally accepted as the minimum effective energy that is required to defibrillate the heart. There have been many differing methods to establish the defibrillation threshold of any one electrode configuration reported in the literature but it appears that there is no single best method of determining the defibrillation threshold. The most important factor when comparing configurations is to ensure that the same method of defibrillation threshold determination is used for each configuration. I elected to use a two-stage defibrillation threshold determination algorithm. The first an arbitrary midpoint starting energy followed by three further shocks in a step up/step down algorithm to determine entry point onto stage two, figure 2.7↵. The second stage an incremental binary search along a therapy ladder with defibrillation attempts determined by the programmability of the device, figure 2.8↵. The defibrillation threshold was defined as the mean of the two successful therapies at the last three reversals. This ensures then that if the DFT varies significantly from the initial starting point then the number of fibrillation/defibrillation cycles taken to reach this point would be reduced. Variations from this protocol are discussed in the relevant chapters' methods section.

2.1.6 Statistical Analysis

The intention was to compare defibrillation characteristics using a paired T test. For protocols in which a group was compared with more than one other group a Bonferroni adjustment was applied. Where the data was not normally distributed non-parametric tests were used and are discussed in the relevant chapters. Also discussed in the relevant chapter are the methods used for correlations.

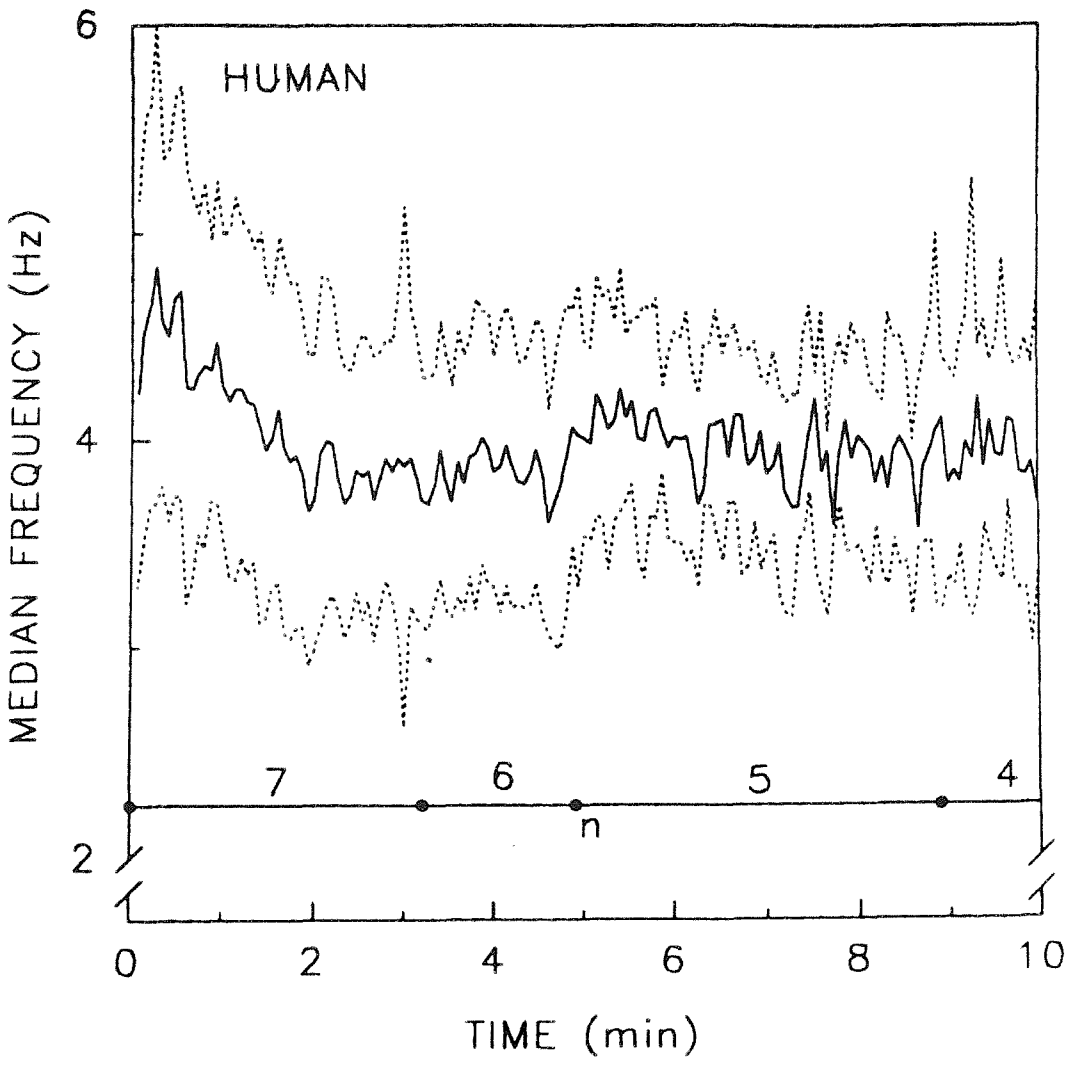
Calculations of significance were made using SPSS, graphics are produced using Excel and SPSS.

Figure 2-1 Ventricular Fibrillation Frequency vs. Time in Swine



Plot of FM (Hz) versus duration of VF (minutes) for eleven swine. The standard deviation depicted by the dotted lines.

Figure 2-2 Ventricular Fibrillation Frequency vs. Time in Humans



Plot of FM (Hz) versus duration of VF (minutes) for seven human subjects. The standard deviation is depicted by the dotted lines.

↵

Figure 2-3: Threshold Voltage (volts) Requirements of the Pig, Man and Dog

Electrode Location	Pulse Duration (ms)	Pig	Man	Dog
S-A Node	1.0	0.36-0.58		0.33-0.65
	0.5	0.58-0.96		0.22-1.14
Atrial Appendage	1.0	0.26-0.60	0.56-1.79	0.33-0.65
	0.5	0.27-1.21	0.46-2.29	0.22-1.14
RV endocardium	1.0	0.15-0.35	0.20-0.61	0.30-0.34
	0.5	0.23-0.51	0.27-0.61	0.41-0.49
LV myocardium	1.0	0.17-0.43		0.26-0.30
	0.5	0.31-0.69	0.43-0.95	0.33-0.39

Figure 2-4 Hemodynamic Comparisons of the Pig and Man.

Parameter	Pig	Human
Heart Rate (BPM)	106 ± 8	87 ± 12
Mean Aortic Pressure (mmHG)	104 ± 4	112 ± 9
LV Systolic Pressure (mmHG)	112 ± 19	112 ± 9
LVEDP (mmHG)	12 ± 1	5.9 ± 2.1
Mean PA Pressure (mmHG)	15 ± 0.6	15.0 ± 4.3
Cardiac Output (L min^{-1})	2.36 ± 0.30	6.3 ± 2.4
Stroke Volume (ml)	20 ± 4	89 ± 30
Temperature (°C)	38.7 – 39.8	36.5 - 37.5

Figure 2-5 Biochemical & Haematological Comparisons of Man and Pig.

Parameter	Pig	Human
Sodium (mmol l^{-1})	135-152	132-144
Potassium (mmol l^{-1})	4.9-7.1	3.3-4.7
Chloride (mmol l^{-1})	94-106	95-105
Magnesium (mg dl^{-1})	1.2-3.7	1.8-2.4
Total Protein (g dl^{-1})	4.8-10.3	6.2-8.2
Albumin (g dl^{-1})	1.8-5.6	3.6-4.7
Total Cholesterol (mmol l^{-1})	1.9-4.3	3.6-6.7
Creatinine (mg dl^{-1})	1.2-6.0	0.6-1.7
Glucose (mg dl^{-1})	55-110	70-110
WBC ($\times 10^9$ l^{-1})	14.8	4.3-10.8
Neutrophils (%)	34.0	40-75
Lymphocytes (%)	55.5	20-45
Monocytes (%)	4.3	2-10
Eosinophils (%)	0.24	1-6
Haematocrit (%)	41.0	42-53
Haemoglobin (g dl^{-1})	12.4	14.0-17.7
RBC ($\times 10^{12}$ l^{-1})	6.99	4.5-6.0
MCV (micron^3)	58.5	80-96
MCHC (g%)	30.2	32-35
pH	7.48 ± 0.006	7.35-7.45
pO_2 (kPa)	10.6-12.7	10-13.3
pCO_2 (kPA)	4.0 - 6.2	4.8-6.1
HCO_{3-} (mmol l^{-1})	21.2 ± 32.1	22-30

↵

Figure 2-6 Technique of Swine Intubation

(a) The mouth is held wide open and tongue pulled out of the mouth by an assistant, and the laryngoscope inserted; (b) The epiglottis is seen deep in the throat, obscuring the vocal cords; (c) A long instrument flips the epiglottis up out of the oesophagus, towards the hard palate; (d) With the epiglottis held up toward the hard palate by the laryngoscope, the larynx is now visible.

Reproduced from Techniques and pitfalls of anaesthesia and thoracic surgery in the pig(118).

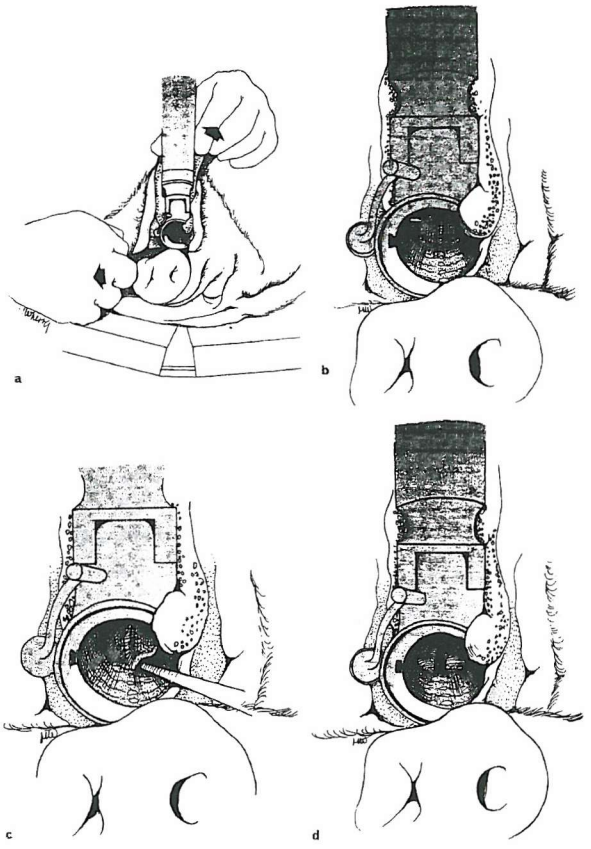


Figure 2-7: Determination of Entry Point onto DFT Determination Pathway

Therapies in Joules
S=success, F=failed defibrillation attempts

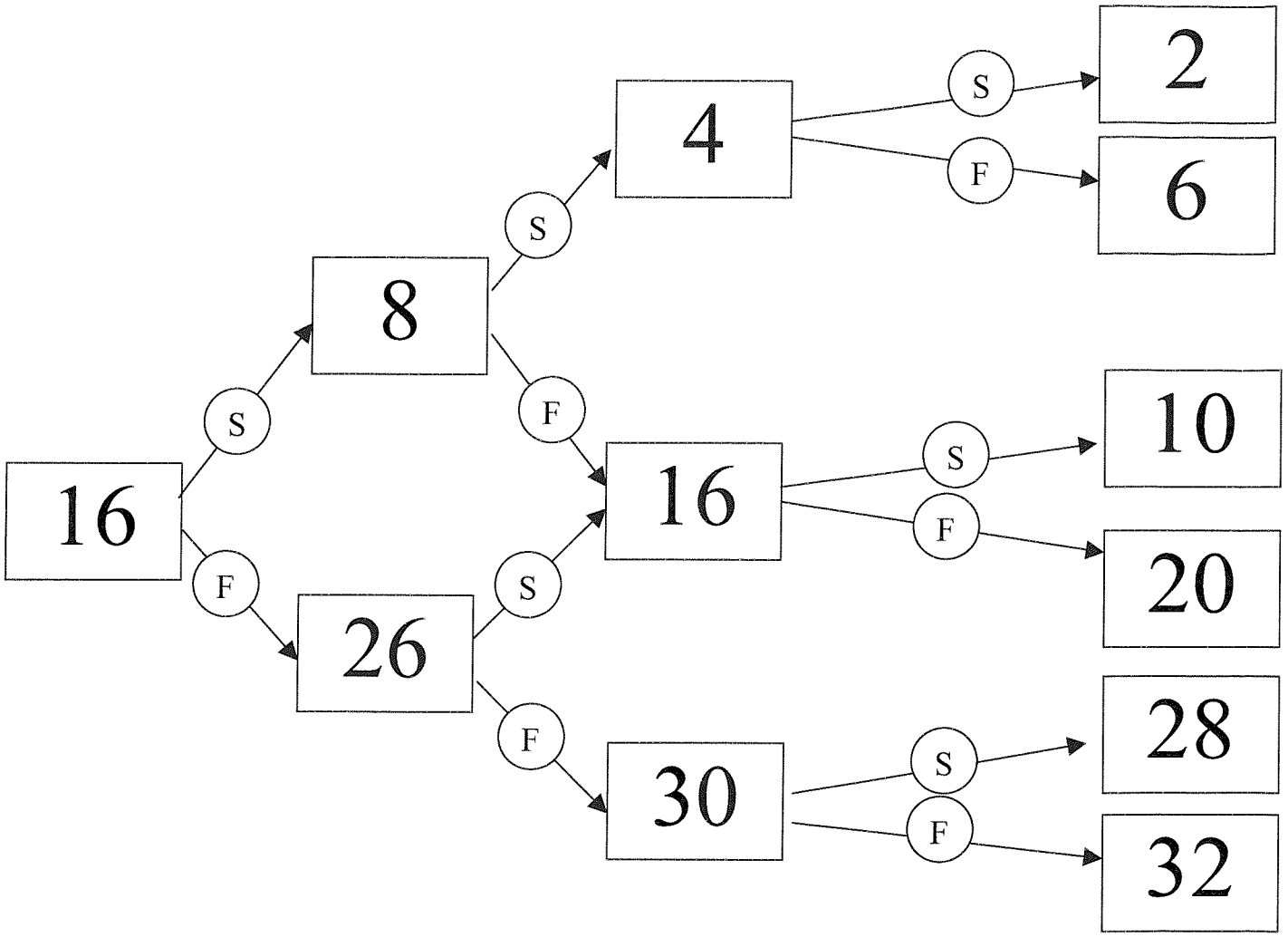
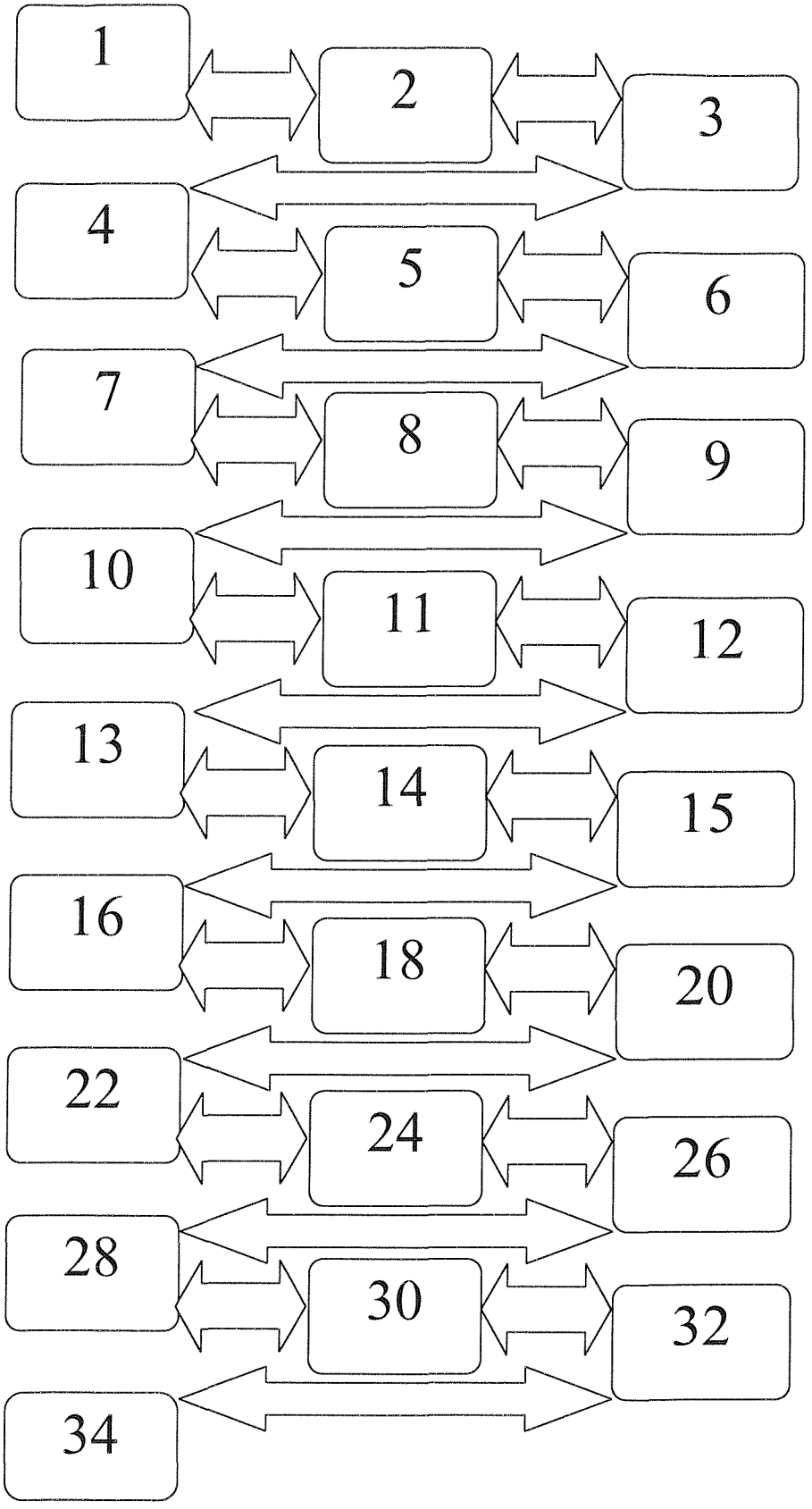


Figure 2-8 Increments Defibrillation Energy in Binary Search Protocol



Increment points (J) available for DFT determination.

2.1.7 Ethical Considerations

The human studies were approved by the local regional ethics committee and Southampton University Hospitals Trust Research and Development Directorate. Issues with the potential to cause ethical objections are: the instrumentation of coronary sinus in a patient who would not otherwise require it and the additional time in ventricular fibrillation as a result of two defibrillation threshold determinations.

Instrumentation of coronary sinus is in fact extremely safe(119), the time in ventricular fibrillation was limited by performing a three shock threshold determination algorithm.

2.1.8 Lead Design

A defibrillation electrode was custom designed for the studies. Factors identified as desirable were: narrow external dimensions, 50 ± 5 mm length defibrillation coil, largest possible surface area of defibrillation coil, over-the-wire positioning capability and a flexible shaft to navigate tight bends.

The lead provided had a 55 mm length, 334 mm^2 surface area, Platinum-Iridium alloy (80/20) defibrillation coil and a polyurethane insulation. The external dimensions were 1.45 mm (4.4F) allowing it to pass through an 8F introducing catheter figure 2.9. The lead could be placed over-the-wire↵. The micro filament electrodes used and described in protocol 3.1 are also shown, figure 2.10↵.

2.1.9 Implant Description

Patients were sedated with intravenous midazolam and diamorphine, a left sub pectoral pocket was fashioned and two haemostatic sheaths placed in the left subclavian vein. A dual coil defibrillation lead was advanced so the distal coil tip was at the right ventricular apex and the proximal coil was in the superior vena cava. An 8F multipurpose hook catheter was manipulated into proximal coronary sinus and the lead placed in the appropriate tributary. Initially connections were made through an external junction box

(Medtronic 5421) and therapies delivered from an external defibrillator (Medtronic 5358). This presented practical difficulties with sterilisation and from later in the first protocol therapies were delivered from the implanted defibrillator. For the second human protocol the same defibrillator was used in all patients to standardise detection, charge times and waveform.

After determination of defibrillation threshold in the relevant configurations the coronary venous lead and catheter were removed and the sheath used to place the atrial lead if indicated. The remainder of the implant procedure was then completed.

2.1.10 Monitoring Induction and Defibrillation

External ECG was monitored in lead II and non-invasive blood pressure recorded at five-minute intervals. Non-invasive arterial oxygen saturations were monitored continuously.

Ventricular fibrillation inductions were performed by delivery of five second bursts of AC current, in cases where the external defibrillator was used fibrillation was confirmed and the appropriate strength defibrillation attempt administered. When the implanted defibrillator was used the device default auto-detection was used to trigger therapy. In all cases biphasic wave forms with capacitive tilt were used as in clinical practice. Failed attempts were followed by maximum output rescue shocks.

2.1.11 Defibrillation Threshold Determination

Defibrillation threshold was determined by a three shock binary search, figure 2.11↵, the order of testing of configurations was randomised, programmed and delivered energy, impedance and result were recorded for each shock.

2.1.12 Statistical Analysis

Defibrillation characteristics were compared using a Paired T test. A two sided p value of 0.05 or less was considered significant.

Figure 2-9 Coronary Venous Defibrillation Electrode Lead Design

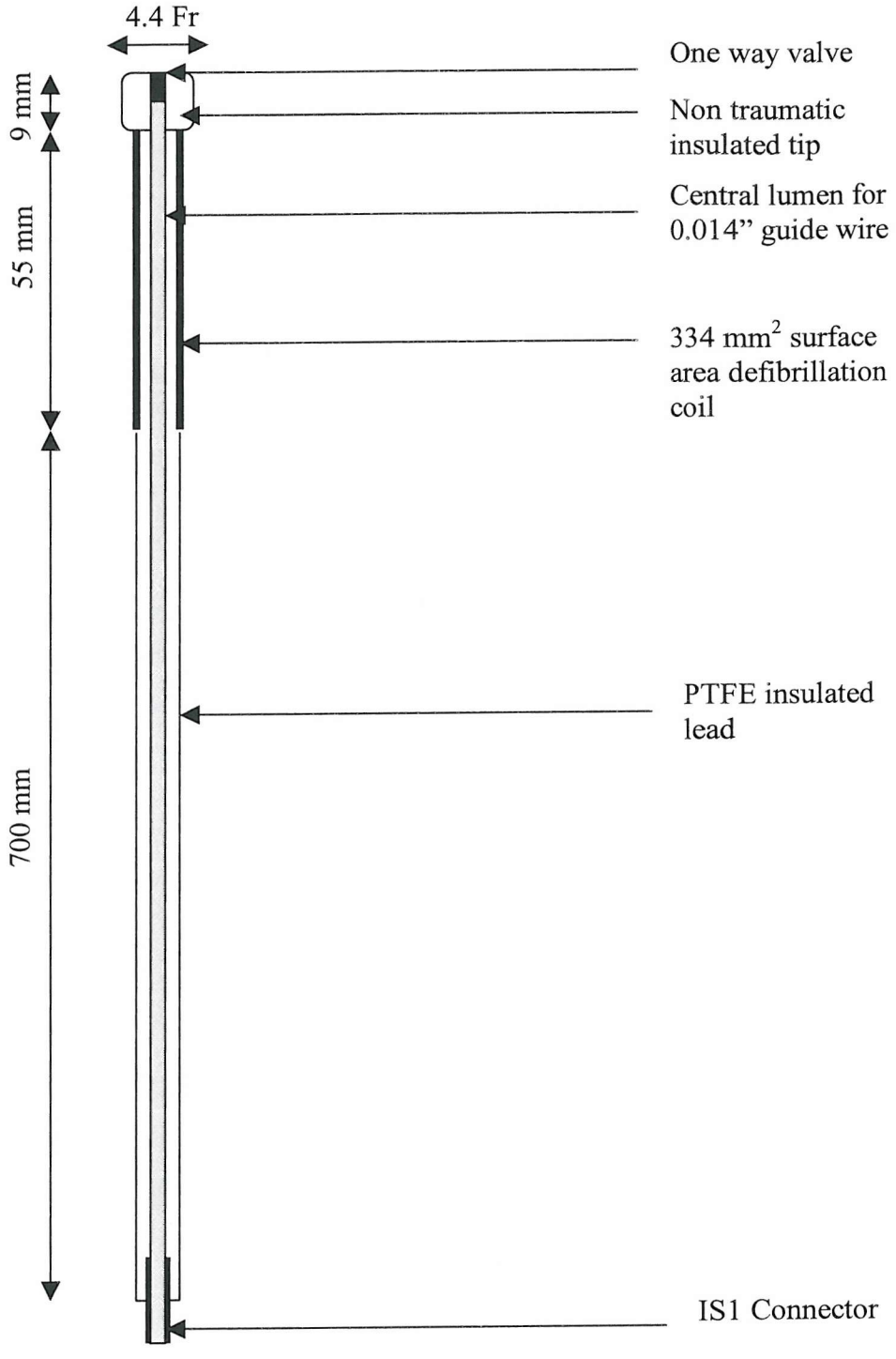


Figure 2-10 Micro Filament Electrode Lead Design

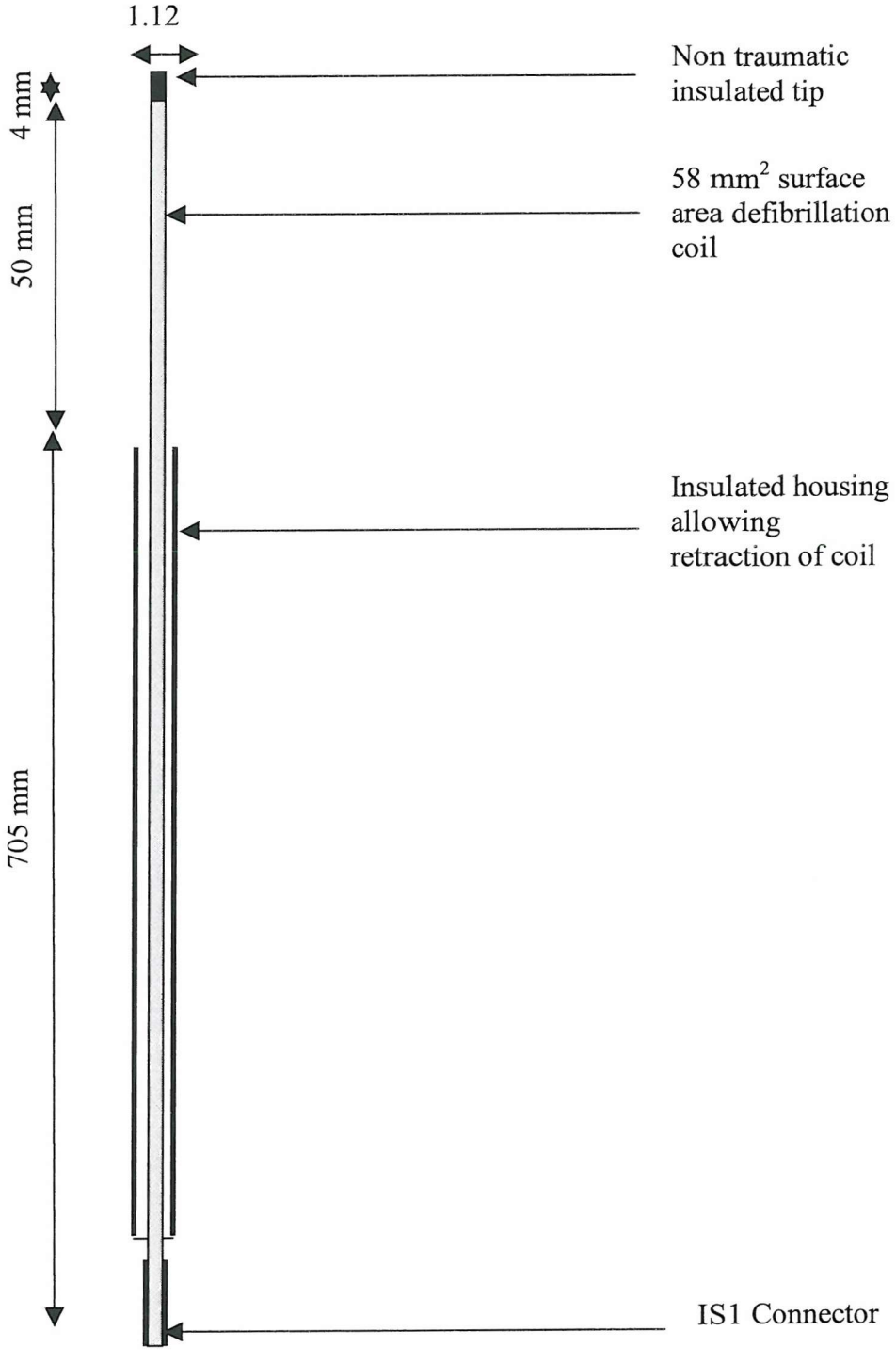
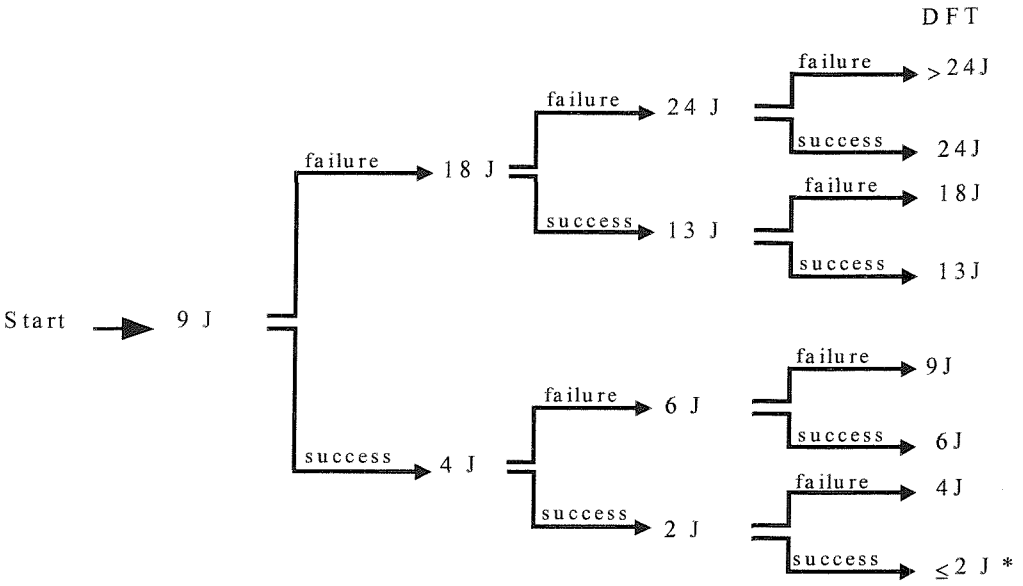


Figure 2-11 Defibrillation Threshold Determination Algorithm for Human Studies



3 ANIMAL STUDIES OF DEFIBRILLATION

3.1 An Evaluation of the Passive Electrode Affect Through Dual-filament Middle Cardiac Vein Defibrillation in Pigs

3.1.1 Abstract

Introduction: Bystander epicardial patch electrodes may increase defibrillation threshold in conventional systems by a passive electrode affect. Such an affect has never been demonstrated to decrease defibrillation threshold nor to be exerted by transvenous electrodes. *Aims:* (i) To investigate whether a passive electrode affect decreases defibrillation threshold (DFT) in multi-filament middle cardiac vein (MCV) defibrillation. (ii) To validate a novel micro-filament electrode in auxiliary MCV defibrillation. (iii) To validate the same electrode in sole anodal defibrillation. *Methods:* 12 pigs underwent active housing (AH) insertion, with defibrillation coils placed transvenously in right ventricular (RV) apex and superior vena cava (SVC). MCV was cannulated and 1.12F, 50 mm coil electrodes (Ela Medical) deployed in right and left branches. Lead placement was possible in 11 of 12 animals. DFT (J, mean ± SD) was determined by three reversal binary search and compared between 3 pairs of configurations. *Results:* (i) MCV monofilament (single filament deployed) to AH (25.9 ± 10.9) vs. MCV mono + passive filaments (both filaments deployed, 1 connected) to AH (19.9 ± 11.4), 24% DFT reduction p=0.008 (ii) RV to SVC+AH (18.5 ± 7.3) vs. RV+MCV to AH (12.9 ± 5.8), 30% DFT reduction p=0.021 (iii) RV to AH (19.4 ± 6.8) vs. MCV bi-filament (both filaments deployed and connected) to AH (20.1 ± 11), no difference p=0.688. *Conclusion:* a bystander electrode adjacent to a mono-filament electrode in MCV reduces DFT by 24% compared to monofilament MCV alone. Micro-filament electrodes decrease DFT, compared to conventional configurations, as auxiliary anode but not as sole anode.

3.1.2 Introduction

The passive electrode affect is the influence of an electrode that is not connected to a circuit (a bystander electrode) on that configuration's defibrillation characteristics. It has been demonstrated that bystander epicardial patch electrodes increase defibrillation threshold (DFT), through a passive electrode affect, when shocking from transvenous systems(99;104). This effect does not appear to be replicated in bystander endocardial leads(87) and it has never been shown that the passive electrode affect may be used to decrease DFT.

Implantable cardioverter defibrillators (ICD) are an accepted treatment for primary(19-21) and secondary(22-24) prevention of life threatening ventricular arrhythmias.

Evaluation of factors leading to a decrease in DFT may yield advantages in clinical application of ICD: failure rate will be reduced through an increase in safety margin (the difference between DFT and maximum output of device), device size and longevity will be improved through the benefits of a lower DFT on battery and capacitor design.

The middle cardiac vein (MCV) has the potential to offer low DFT compared with conventional endocardial systems through its' anatomical location(90). It has been evaluated in animal(53-55;81) and human(103) studies.

3.1.3 Aims

To investigate whether a passive electrode affect may decrease DFT in multi-filament MCV defibrillation using a novel microfilament electrode.

To validate this novel microfilament coronary venous defibrillation electrode as an auxiliary electrode.

To validate the novel electrode in sole coronary venous anodal defibrillation.

3.1.4 Methods

12 female pigs (weight 53.1 ± 10.0 kg) were prepared and anaesthetised as described previously. A dual coil defibrillation lead (Sprint Quattro®, Medtronic, MN, USA) was advanced to RV apex and SVC. MCV was catheterised with an 8F MPA1 catheter cut to 58 cm. Custom designed microfilament electrodes (1.12F with 50 mm length 58 mm^2 surface area coils, ELA medical SA, Fr) were introduced into left and right branches of MCV. An active housing was inserted subcutaneously in the left pectoral area (Defender®, ELA medical). Electrodes were connected through a junction box to an external defibrillator (5358, Medtronic, MN, USA). Induction of VF was by 5 s 50Hz AC current application, defibrillation attempts were performed with a biphasic waveform with capacitive tilt. DFT determinations were performed as previously described.

Statistical Analysis, although six configurations were studied, *figure 3.1* ⏎, statistical analysis for a difference between configurations was performed only between pairs of interest. To examine the passive electrode affect a comparison was made between MCV (mono)→AH and MCV (mono + passive)→AH. To validate the novel electrode in auxiliary defibrillation RV+MCV→AH was compared with RV→SVC+AH. To assess the multifilament electrode in sole anodal defibrillation MCV→AH was compared to RV→AH.

In studies of DFT it is conventional to compare values by a paired T test. In this protocol there were several instances of 34 J DFT values being allocated because animals were not successfully defibrillated in the configuration concerned. The DFTs were not therefore normally distributed making parametric testing inappropriate. For this reason the more rigorous non-parametric Wilcoxon signed rank test was used to assess significance. For each of the comparisons a two sided p value of 0.05 or less was considered significant.

3.1.5 Results

Placement of a bi-filament electrode was possible in eleven out of twelve animals. In one animal MCV could not be selectively catheterised. Screening time for procedure was 13.4 ± 6.4 minutes. The DFTs and impedances of the configurations, *figures 3.2-5* ↵, are shown.

DFT was 24% less in mono-filament + passive than mono alone to AH, p=0.008. The DFT of RV + MCV to AH was 30% lower than RV to SVC + AH, p=0.021. There was no difference in DFT between MCV (bi-filament) to AH and RV to AH p=0.688.

The electrical properties of the micro-filaments were atypical: at high energy outputs their impedance increased substantially preventing efficacious defibrillation in some animals for configurations involving micro-filaments as sole cathode *figure 3.6*↵.

Autopsy was performed at end of procedure. No macroscopic damage was seen to myocardium or pericardium.

3.1.6 Discussion

The anatomical site of electrodes alters the shocking vector and affects the DFT either by allowing inclusion of a critical mass of myocardium(42) (the septum is an important region(90)), or by permitting simultaneous depolarisation of all myocardium with sufficient energy to prevent recurrence of fibrillation(44;120). A higher DFT will result if energy is distributed unfavourably; the converse is a lower DFT with optimal electrode placement(90;121;121).

Defibrillation configurations involving epicardial patch electrodes were superseded by transvenous systems due to the lower complication rate of the latter(98). This came at the cost of an increased DFT(121). An electrode placed transvenously but having the low DFT of the epicardial patch electrodes would combine the advantages of epicardial patch electrodes and transvenous systems.

Possible reasons for the lower DFT seen with epicardial patches are: anatomical site (infero-septal); epicardial location; large electrode surface area; broad area of myocardium in contact with the distal electrode(65).

Defibrillation electrode placement in MCV may decrease DFT(53;121) because of its infero-septal epicardial location. Placement of multiple defibrillation filaments is feasible(54;121) and gives further theoretical advantages by increasing the surface are of the electrode and broadening the myocardium in contact with the distal electrode. Placement of multiple filaments increases complexity of implantation partly by necessitating multiple proximal connections: the passive electrode affect might be used to reduce this complexity.

After observations that bystander epicardial patches increase DFT through a passive electrode affect, but no equivalent influence on DFT is exerted by transvenous shocking coils or pacing leads, the phenomenon received no further research attention. We have

shown the passive electrode exerted by a bystander MCV coil in the adjacent radicle to an identical active coil decreases DFT by 24%.

The ability of a bystander electrode to exert a passive electrode affect is dependant on the proportion of current that is drawn through the alternative route. This is a function of the impedance of the intended configuration compared to the impedance of the parallel circuit created by the bystander electrode and intervening tissue. Epicardial patches have lower impedance than transvenous coils allowing current shunting and a passive electrode affect: two transvenous coils have similar impedance minimising current shunting. Furthermore an electrical passive electrode affect may only influence DFT if it significantly alters shocking vector, in the case of bystander epicardial systems current is drawn in the opposite direction from the anode: predictably DFT is increased. In transvenous systems the intended and bystander coils occupy similar anatomical sites: the vector is not greatly altered even if a passive electrode affect exists on electrical properties. The impedance characteristics of the micro-filament electrodes used were unusual in that they were high and rose further with increasing current. This creates a situation where the actively connected electrode has a higher impedance than the bystander favouring current shunting and a passive electrode affect. The placement of the two filaments, in the branches of the MCV adjacent to the septum, caused any current shunted to be to a site that is likely to improve current distribution (a virtual composite electrode, the connected and passive electrode, with a greater surface area and broader area of myocardium involved is created).

Placement of multiple filaments in the MCV radicles allows close mimicry of epicardial patch electrode: the anatomical equivalence of MCV with multiple filaments simulating the structure and current distribution. Utilizing the passive electrode affect to avoid multiple proximal connections reduces the complexity of such a system.

For the passive electrode affect to be a clinically useful phenomenon lead configurations taking advantage of it must be safe, stable and transvenously deployed. It would be required to either reduce DFT by over 50% or significantly reduce the variability of DFT.

We have shown that the branching structure of coronary sinus tributaries (already widely utilised in pacing and validated in acute defibrillation studies(103) is a suitable site to explore the uses of the passive electrode affect in transvenous defibrillation. The electrical properties of the microfilaments made them unsuitable as sole anode as there impedance increased preventing effective defibrillation in certain individuals, it was however effective as an auxiliary anode.

Limitations of the study, three bystander electrodes present in this study were not examined for a passive electrode affect, the RV, SVC and MCV coils were all left in place for configurations that did not involve them. They are less likely to exert a passive electrode affect given their distance from the active circuit and were constant in the MCV mono and mono + passive configurations.

The magnitude of the DFT reduction would not be clinically useful and, the configuration used was demonstrated not to be reliable for the reasons discussed.
It is not certain that findings from any animal study can be replicated in humans: discordance in findings between prior porcine and human MCV defibrillation studies(53;55;103) (possibly explained by the anatomical difference in the mediastinal orientation between the species) has been seen.

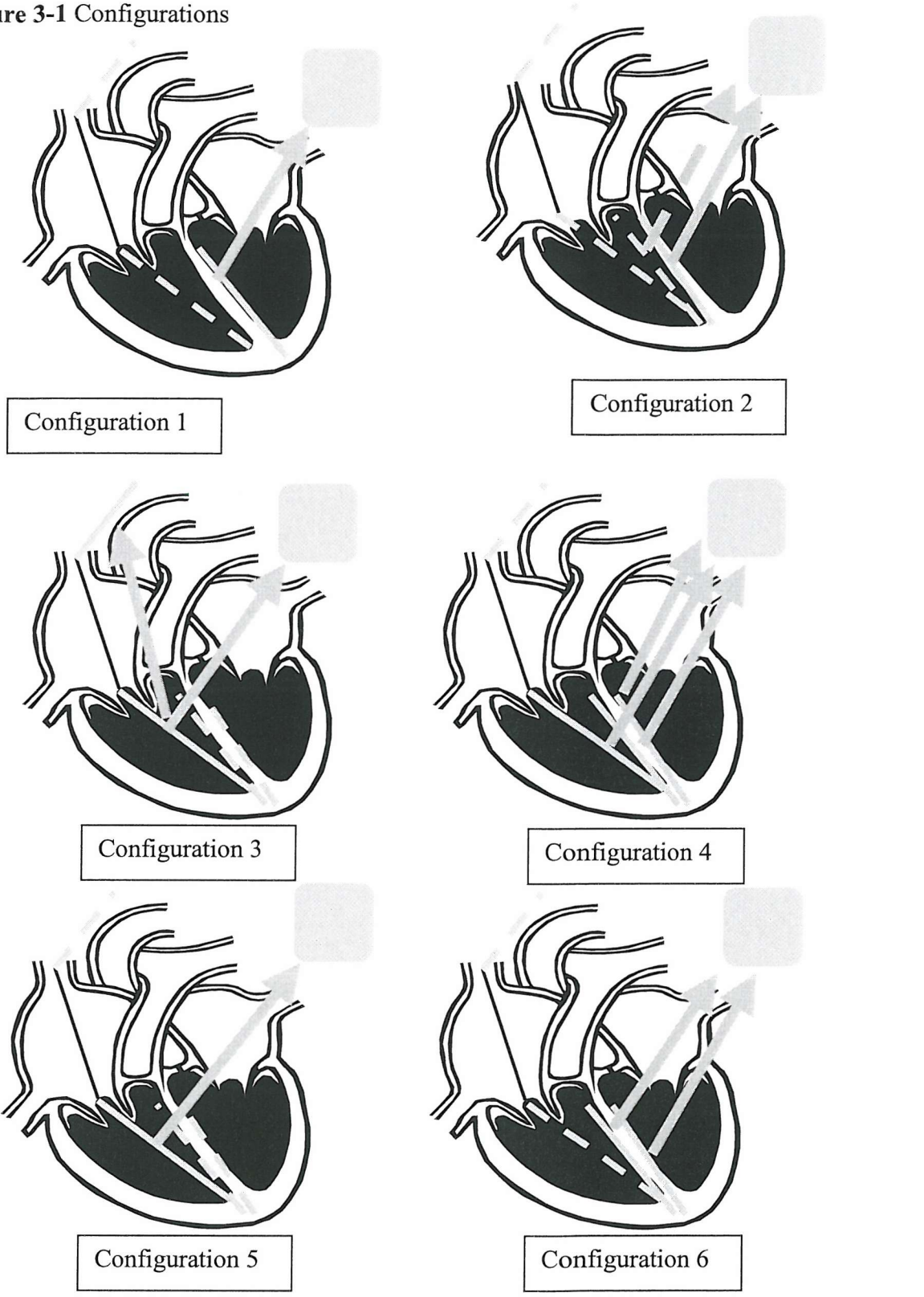
In this case however the model, anatomical site and magnitude of effect are secondary to the proof of concept: a passive electrode affect may reduce DFT.

3.1.7 Conclusion

In a porcine model, with transvenously placed coronary venous leads, a passive electrode affect decreases DFT and impedance when shocking to an active housing. The

novel microfilament electrodes decrease DFT when employed as an auxiliary anode but are not reliable in sole anodal defibrillation.

Figure 3-1 Configurations



Configurations
1 MCV mono filament to AH (1 filament deployed and connected), 2 MCV mono + passive to AH (2 filaments deployed, 1 connected), 3 RV to SVC and AH
4 RV + MCV to AH, 5 RV to AH, 6 MCV bi filament to AH (2 filaments deployed, 2 connected)

Insulated Connection
Active electrode
Bystander electrode

Passive vector
Active vector
Active housing

Figure 3-2 Summary Results by Configuration

Anode	Cathode	DFT (J) ± SD	Impedance (Ω) ± SD
MCV mono	AH	25.9 ± 10.9	83.8 ± 34.8
MCV mono + passive	AH	19.9 ± 11.4	72.5 ± 26.9
RV	SVC+AH	18.5 ± 7.3	41.5 ± 5.6
RV+MCV	AH	12.9 ± 5.8	42.3 ± 5.4
RV	AH	19.4 ± 6.8	48.4 ± 5.8
MCV bifilament	AH	20.1 ± 11.0	64.3 ± 15.3

Figure 3-3 DFT MCV monofilament to AH vs MCV monofilament + passive to AH

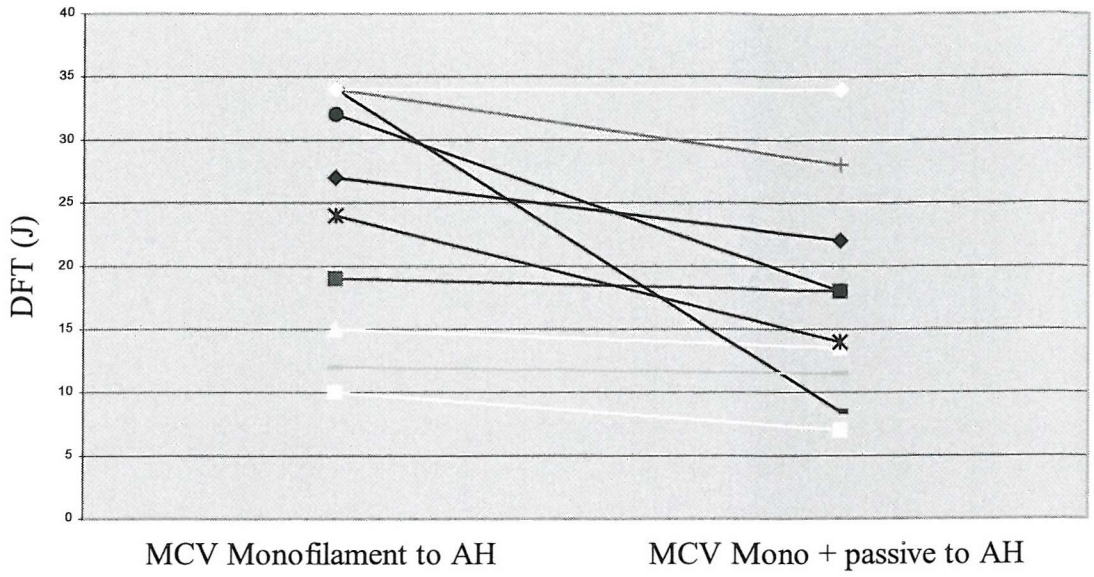


Figure 3-4 DFT RV to SVC + AH vs DFT RV + MCV to AH

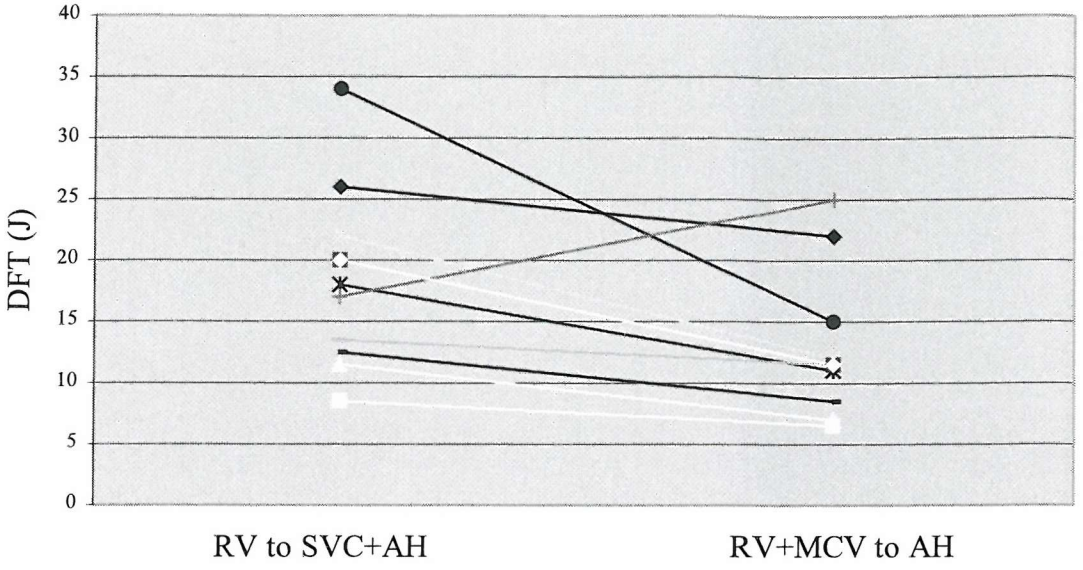


Figure 3-5 DFT RV to AH vs DFT MCV bi-filament to AH

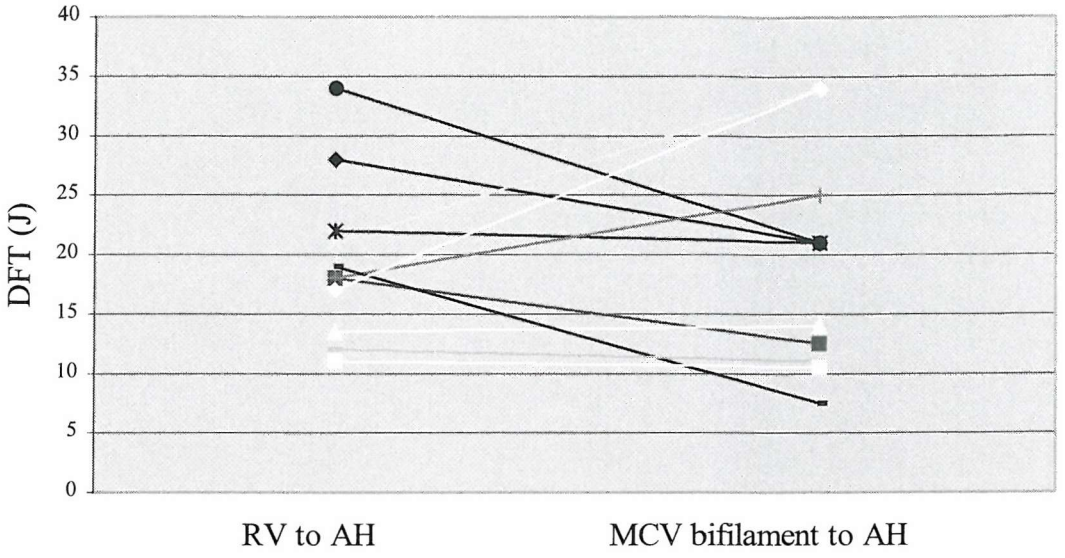
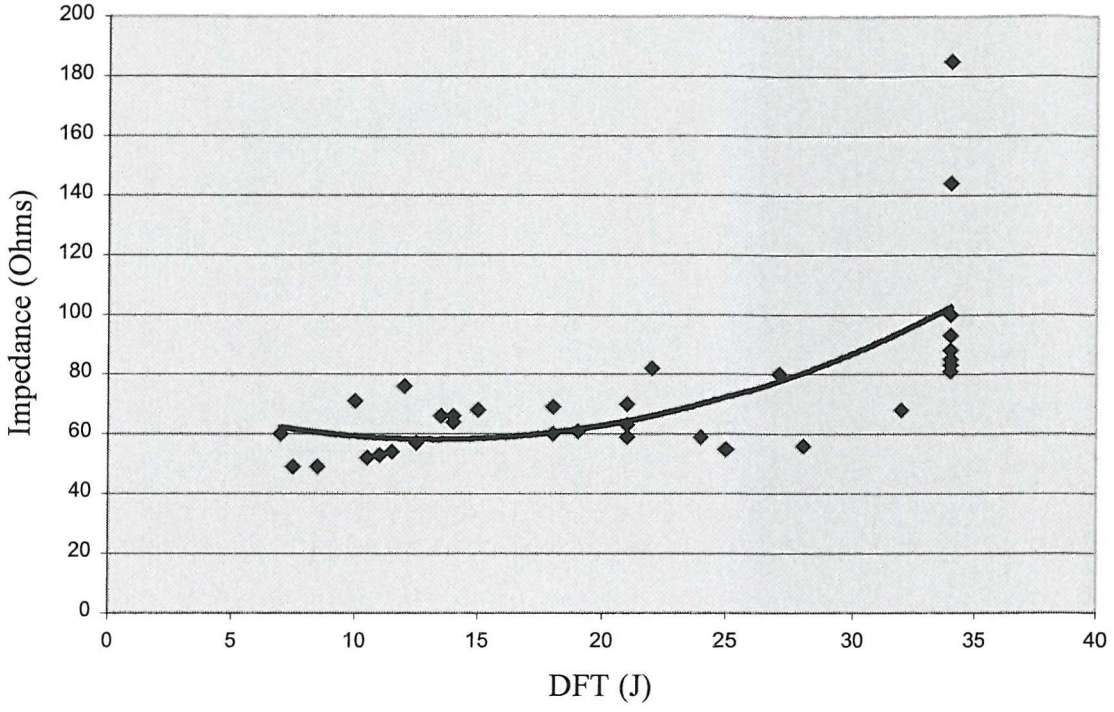


Figure 3-6 Impedance vs DFT for MCV sole anodal configurations



3.2 Comparison of Sole with Auxiliary Middle Cardiac Vein Defibrillation

3.2.1 Abstract

Introduction: The middle cardiac vein (MCV) has been validated in pigs as a site for defibrillation lead placement and compares favourably with right ventricular (RV) lead positioning. It has not previously been shown that RV + MCV and MCV alone are equivalent when shocking to a conventional superior vena cava (SVC) + active housing (AH) cathode. Aims: (i) To validate a novel coronary venous defibrillation electrode (ii) To compare auxiliary and sole anodal middle cardiac vein defibrillation *Method:* 12 pigs were anaesthetised and had an AH (Defender IV, Ela Medical) implanted in the left sub pectoral region. The right jugular vein was accessed by cut down and defibrillation coils (Swift, Ela Medical) placed at RV apex and in SVC. The MCV was then engaged with a 9 F MPA1 catheter and position confirmed by contrast venography. A custom designed defibrillation coil (Ela Medical) was advanced into MCV. The DFT for 3 anodes (RV; RV+MCV; MCV) to SVC + AH was then assessed by a 3 reversal binary search method. The order of testing was randomised, inductions (5 second 50 Hz ac) and defibrillations were delivered through an external generator (5358, Medtronic). *Results:* Both MCV ($p<0.001$) and RV + MCV ($p<0.001$) yielded significantly lower DFT than RV. There was no difference between MCV and MCV + RV ($p=0.67$). *Conclusion:* With appropriate lead design defibrillation configurations that do not involve crossing any heart valve may produce low DFT compared to conventional configurations.

3.2.2 Introduction

Implantable cardioverter defibrillators (ICD) are established in the primary(19-21) and secondary(22-24) prevention of life threatening ventricular arrhythmia.

The middle cardiac vein (MCV) has been demonstrated in animal(54;55) and human studies as a site with the potential to yield a low defibrillation threshold (DFT), comparable to that of epicardial patch electrodes, through a lead placed transvenously. Previous investigations have compared MCV as either sole anode or auxiliary anode with conventional right ventricular (RV) anodal defibrillation(53-55;103;106). A direct comparison of defibrillation characteristics between an MCV anode and an MCV + RV anode using low impedance coils and shocking to a superior vena cava (SVC) + active housing (AH) cathode has not been undertaken.

We investigated the defibrillation characteristics of three anodes; RV: RV + MCV: MCV in defibrillation when paired with a conventional SVC + AH cathode.

3.2.3 Aims

To validate a novel coronary venous defibrillation coil

To compare auxiliary with sole anodal middle cardiac vein defibrillation

3.2.4 Methods

12 large white cross female pigs (38.7 ± 1.4 kg) were prepared and anaesthetized as described previously. Defibrillation coils (Swift®, Ela Medical SA, Fr) were advanced to RV apex and SVC. MCV was catheterised with a 58 cm 9F MPA1 catheter. A custom-designed electrode (MP35N: 4.7Fr, 55 mm length 386 mm^2 SA, Ela Medical, Fr) was introduced into MCV. An "active housing" was inserted subcutaneously in the left pectoral area (Defender®, Ela Medical). Electrodes were connected through a junction box to an external defibrillator (5358, Medtronic, MN, USA). DFT determinations were performed as described previously.

Three anode configurations were studied; (i) MCV; (ii) MCV + RV; (iii) RV. The cathode was SVC + AH for all anodes. The order of testing was randomised.

Statistical analysis: paired T tests were used to compare defibrillation characteristics between configurations. A Bonferroni adjustment was applied giving a threshold of $p<0.017$ as statistically significant.

3.2.5 Results

Screening time for the procedure was 3.2 ± 2.8 min, lead placement was possible in all animals.

The no difference in DFT was observed between MCV (7.5 ± 1.68 J) and MCV + RV anodes (7.33 ± 1.72 J) p=0.67.

Both of MCV configurations had lower DFT than RV to SVC + AH (13.8 ± 4.33 J); MCV 46% reduction p=0.001; MCV + RV 47% reduction p=0.001, *figure 3.7; 3.8*↵.

Impedances were; RV 40.5 ± 3.4 Ω; RV + MCV 33.3 ± 6.0 Ω; MCV 51.1 ± 22.6 *figure 3.9*↵. This represented a 18% decrease between RV + MCV and RV, (p=0.008) and a trend toward a 35% lower impedance in RV + MCV than MCV (p=0.023). There was no significant difference between RV and MCV, p=0.131.

3.2.6 Discussion

Exploring novel sites of defibrillation may reduce the DFT (or variability of DFT) and permit the design of smaller, longer lasting devices with lower failure rates. Such novel sites may also allow added functions to the novel lead, in the case of coronary veins cardiac resynchronisation therapy (CRT) and anti tachycardia pacing (ATP). Alternative sites to RV endocardium may have other advantages through being implantable in patients with morphologically abnormal RV cavities or tricuspid valves.

A higher DFT is seen with transvenous endocardial compared with epicardial patch systems(121). Explanations for this may be related to the structure of the patch or the

epicardial position. From the hypothesis that the epicardial position is at least partly responsible for the low DFT, coronary veins become attractive as an epicardial transvenously accessible site.

Previous studies have demonstrated superiority of MCV over RV defibrillation in the porcine model(53-55;106) These studies demonstrated its safety on the surrounding myocardium and pericardium with no myocardial necrosis on autopsy. The MCV is shown to be an efficacious and safe route of defibrillation in man.

The explanation for the lower DFT in MCV defibrillation is likely to be that the shocking vector directly encompasses more myocardium(42), particularly septum which may be an important target(90). It has been argued that an improved shocking vector will allow depolarisation of all myocardium at sufficient energy to prevent re-induction of ventricular fibrillation (VF) but at a lower total energy dose(44;120).

Other studies of coronary venous defibrillation have been based on the hypothesis that the low current delivery to the left ventricular (LV) lateral wall is a potential contributing factor failed defibrillation. These workers have therefore targeted this area with auxiliary shocks(101;102). MCV to SVC + AH has a vector that includes a greater proportion of myocardium than RV to SVC + AH(90) justifying its use in single anodal defibrillation as previously demonstrated(54). A potential obstacle to single coil anodal MCV defibrillation is the concern that energy delivery may be less effective than through conventional coils(122;123). Indeed a human MCV defibrillation study demonstrated that MCV + RV to AH yielded lower DFT for current than RV to SVC + AH but that DFT for energy levels were similar due to the higher impedance of the novel configuration(103).

In this study we have demonstrated that an MCV stand alone anode has the same DFT as a composite RV + MCV anode despite tending to have higher impedance. The findings of previous porcine studies that anodes containing MCV exhibit a lower DFT that RV alone have also been confirmed.

This finding allows the study of stand alone coronary venous anode defibrillation systems. Such systems (a) have no requirement to traverse tricuspid valve (b) may offer a defined maximum DFT. This has the potential advantage of being implantable in patients with morphologically abnormal RV - a group at high risk of life threatening ventricular arrhythmia(32).

It may also allow the development of coronary venous LV pace/defibrillation leads for cardiac resynchronisation therapy (CRT). Patients undergoing CRT ICD implantation would be an ideal group on which to trial coronary venous defibrillation as they are undergoing a clinical coronary sinus procedure.

In human studies catheterisation of MCV has been more challenging than in porcine trials, however should MCV become a clinical site operator experience would increase and reduce the procedure time.

Limitations of the study, This is an acute study using a porcine model and the long term safety and stability of these configurations has not been demonstrated. Mediastinal orientation is different in humans from the pig and requiring separate validation of novel configurations.

For the MCV stand alone configuration to be a valid alternative to traversing tricuspid valve a pace/sense function of the lead would be required as modern devices operate complex discriminatory algorithms to reduce inappropriate therapy as well as deliver effective ATP and bradycardia therapy.

3.2.7 Conclusion

Coronary venous defibrillation with no active RV lead reduces DFT by 46% compared conventional RV defibrillation in this acute porcine study.

There is no difference in DFT between MCV alone and MCV + RV in shocking to a conventional cathode.

↵

Figure 3-7 DFT and impedance by configuration

Anode	Cathode	DFT (J)	SD, DFT	Impedance (Ω)	SD, impedance
RV	SVC + AH	13.8	4.3	40.5	3.4
RV + MCV	SVC + AH	7.3	1.7	33.3	6
MCV	SVC + AH	7.5	1.7	51.1	22.6

Figure 3-8 DFT (J) by Configuration

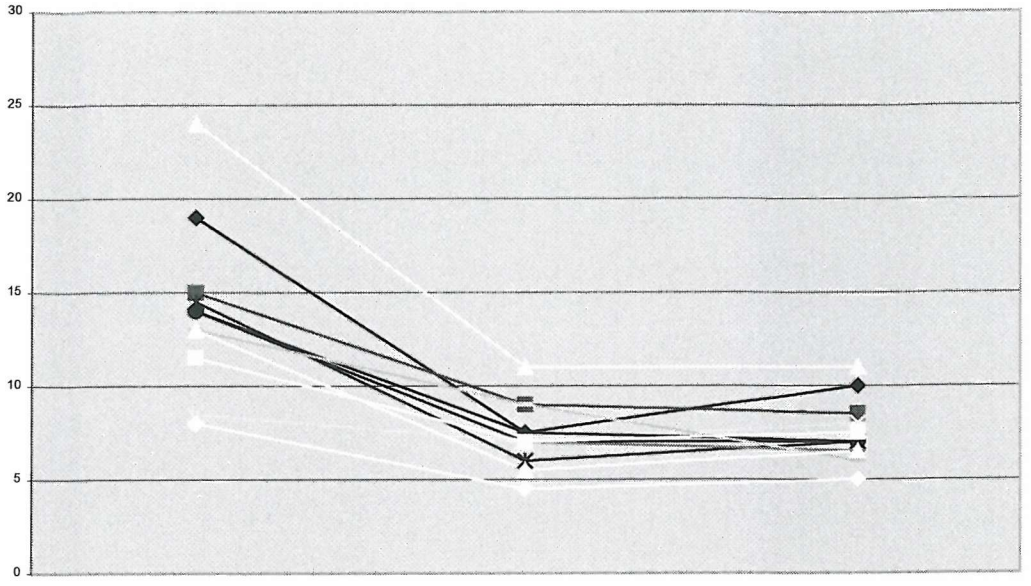
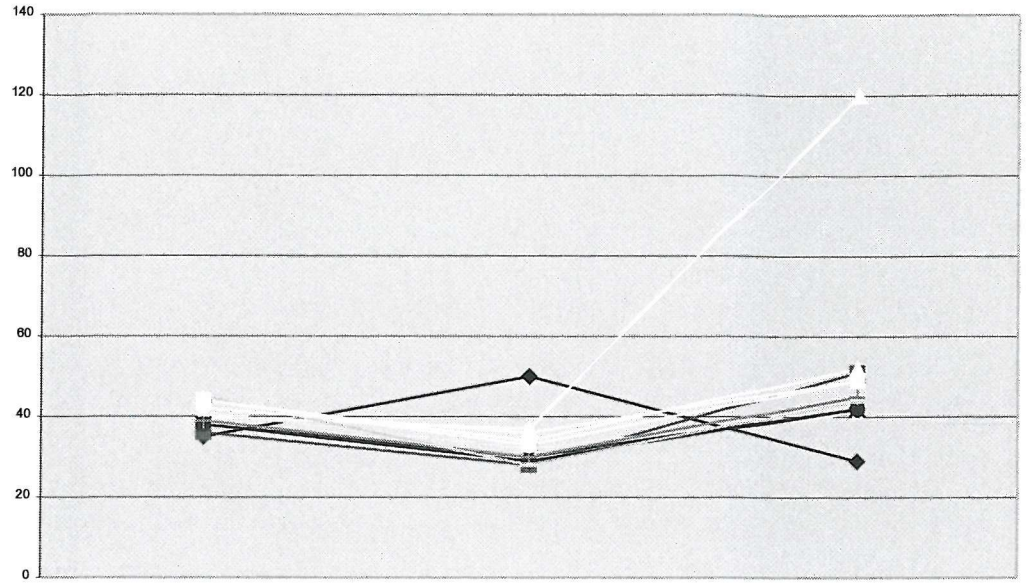


Figure 3-9 Impedance (Ω) by configuration



3.3 The Passive Electrode Affect of Bystander Middle Cardiac Vein Leads in Right Ventricular Endocardial Defibrillation

3.3.1 Abstract

Introduction: Abandoned epicardial patches on the base of the heart have been shown to increase defibrillation threshold, by exerting a passive electrode effect, when defibrillating through conventional transvenous systems with right ventricular (RV) leads. *Aim:* to investigate whether a transvenously placed coronary venous defibrillation coil occupying a basal epicardial position would exert a similar effect. *Methods*: Seven pigs (37.9 +/- 1.1 Kg) were anaesthetised and had an active housing (AH) (Defender IV, ELA medical) implanted in the left sub pectoral region. The right jugular vein was accessed by cut down and defibrillation coils (Swift, ELA medical) placed at RV apex and in superior vena cava (SVC). The middle cardiac vein was then engaged with a 9 Fr MPA1 catheter and position confirmed by contrast venography. A custom designed defibrillation coil (ELA medical) was advanced into middle cardiac vein. The defibrillation threshold was then assessed by a 3 reversal binary search method for the conventional configuration RV to SVC + AH with and without an middle cardiac vein defibrillation coil in place. The order of testing was randomised, inductions (5 second 50 Hz ac) and defibrillations were delivered through an external generator (5358, Medtronic). Defibrillation threshold and impedance were compared using a paired T test. *Results:* There were no differences in defibrillation characteristics between the two groups. C*onclusion:* In a porcine model there is no evidence that a defibrillation coil placed in the mid cardiac vein will affect the defibrillation threshold of a shock therapy delivered from the RV.

3.3.2 Introduction

The only configurations in which a passive electrode affect on defibrillation threshold has been shown to exist have involved epicardial electrodes. Two previously discussed studies demonstrated that a bystander epicardial patch electrode increases defibrillation threshold when shocking from endocardial coil electrodes(99;104). Section 3.1 of this thesis also demonstrated a passive electrode affect with epicardial electrodes, this time the passive electrode affect decreased defibrillation threshold and was exerted by coil electrodes. It previously been demonstrated that bystander endocardial coils do not exert a consistent passive electrode affect on defibrillation threshold(87) despite anecdotal evidence to the contrary.

From section 3.2 of this thesis it would appear with the electrode used the middle cardiac vein is a promising site for defibrillation coil placement. If this electrode in this site exerts a passive electrode affect increasing defibrillation threshold (as bystander epicardial patches do) this would represent a barrier to its' further development.

3.3.3 Aims

To assess the passive electrode affect of a middle cardiac vein defibrillation electrode on right ventricular endocardial defibrillation.

3.3.4 Methods

Seven pigs, weight 37.9 ± 1.1 kg, were prepared and anaesthetised as previously described.

Defibrillation coils (Swift®, Ela Medical SA, Fr) were advanced to RV apex and SVC. Middle cardiac vein was catheterised with a 58 cm 9F MPA1 catheter. A custom designed electrode (4.7Fr, 55 mm length 386 mm^2 SA, Ela Medical, Fr) was introduced into middle cardiac vein. An active housing was inserted subcutaneously in the left pectoral area (Defender®, Ela Medical). Electrodes were connected through a junction box to an external defibrillator (5358, Medtronic, MN, USA).

Defibrillation threshold testing was performed as previously described for the configuration RV → SVC + Can with and without a bystander middle cardiac vein defibrillation coil. The order of the two defibrillation threshold determinations was randomised. *Statistical analysis:* Defibrillation characteristics were compared using a paired T test. Confidence intervals for differences were calculated at the 95% level.

3.3.5 Results

There was no difference of defibrillation threshold (13.7 ± 4.2 vs. 13.2 ± 4.0 J) p=0.177 or impedance (40.7 ± 2.4 vs. 41.0 ± 3.0 Ω) p=0.522 between the configurations with and without the bystander MCV coil, *figure 3.10-3.11*.

Confidence intervals at the 95% level showed a difference in defibrillation threshold of -0.322-0.678 J and a difference in impedance of –0.877-0.305 Ω.

3.3.6 Discussion

Bystander epicardial patches in the same position as middle cardiac vein exert a passive electrode affect during endocardial defibrillation and bystander middle cardiac vein electrodes exert a passive electrode affect during middle cardiac vein defibrillation. Despite this either middle cardiac vein bystander defibrillation coils exert no passive electrode affect, or such an affect is so small as to be of no clinical significance.

As previously discussed for a passive electrode affect to exist an alternative pathway for current must be created. For such an affect to alter defibrillation threshold the alternative pathway must significantly alter the pattern of myocardial involvement in current flow. In comparing bystander epicardial patch electrodes to middle cardiac vein coil electrodes there is a discrepancy in both size and surface area although positioning is similar. The potential alternative route for current presented by the patch electrode will be of lower impedance and involve more myocardium. The lower impedance will increase the probability of a passive electrode affect existing, the additional myocardium will increase the probability of such an affect altering defibrillation threshold.

In comparing right ventricular to middle cardiac vein defibrillation, bystander middle cardiac vein electrodes are in closer proximity to the active electrode, as current density decreases with distance from a source it is intuitive that the closer the coils the greater the potential affect.

Were a passive electrode affect to be exerted by a bystander middle cardiac vein coil electrode on endocardial defibrillation it would be more likely to increase than decrease defibrillation threshold. This may be predicted by the orientation of the bystander coil in the opposite direction from the active coil than the prime shocking vector and is suggested by the fact that bystander epicardial patch electrodes in a similar anatomical position increase defibrillation threshold.

The middle cardiac vein coil electrode used in this study was identical to that used in the section 3.2. The reason this coil was chosen rather than the micro-filament electrodes that demonstrated a passive electrode affect in section 3.1 was that the latter did not appear to promise clinical utility. Given the high impedance of the micro-filaments they may be assumed to be even less likely to exert a passive electrode affect in the same circumstance. *Limitations of the study*, the relative anatomical positions of middle cardiac vein and a right ventricular apical endocardial electrode are similar in man and pigs the model is imperfect in the reproduction of the overall shocking vector. The numbers in the study are small making p value alone a reflection of risk of type II error, however the narrow confidence intervals for the difference between measurements indicate that any difference is not clinically significant.

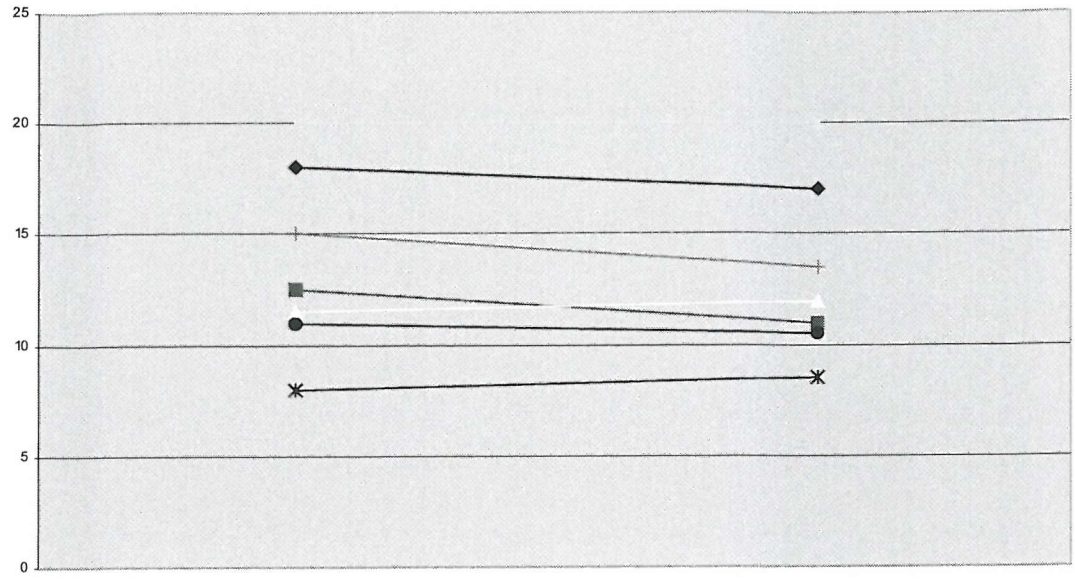
3.3.7 Conclusion

No clinically significant passive electrode affect is exerted by a middle cardiac vein coil electrode on right ventricular endocardial defibrillation.

Figure 3-10 Defibrillation Threshold s and Impedances with and without a Bystander Middle Cardiac vein Electrode

	No MCV		Passive MCV	
Pig	DFT (J)	Impedance (Ohms)	DFT (J)	Impedance (Ohms)
1	18	39	17	38
2	12.5	41	11	41
3	11.5	44	12	44
4	20	37	20	36
5	8	41	8.5	42
6	11	40	10.5	42
7	15	43	13.5	44
Mean	13.7	40.7	13.2	41.0
SD	4.2	2.4	4.0	3.0

Figure 3-11 Defibrillation Threshold With and Without a Bystander MCV Coil



3.4 A Novel Method of Defibrillation Threshold Determination

3.4.1 Abstract

Introduction: Ventricular defibrillation is probabilistic and the value of the defibrillation threshold is a function of the method of evaluation. The gold standard for defibrillation threshold assessment is the binary search method with repeated reversals around the defibrillation threshold. Binary search algorithms require multiple ventricular fibrillation inductions and shocks. In order to reduce these in clinical practice simplified/imprecise algorithms are used. In this study we evaluate a novel method where several test shocks are delivered with increasing energy level in a single ventricular fibrillation induction. *Aims:* (i) To compare the defibrillation threshold values obtained by binary search and the novel protocol. (ii) to establish the reproducibility of the novel protocol (iii) to compare the time in ventricular fibrillation between the binary search and novel protocol. *Methods:* 7 pigs were implanted with an RV/SVC coil and active housing. Defibrillation threshold was assessed for RV→SVC + AH alternately by binary search and the novel method. Each method of defibrillation threshold determination was repeated giving a total of 4 defibrillation threshold determinations (2 binary search, 2 novel protocol). Protocols: binary search, an initial 4 induction/test shock algorithm determining entry onto a incremental step up/down pathway with defibrillation threshold determined by 3 reversals. Novel protocol, a series of 3 inductions each followed by 3 test shocks and a 30 J rescue shock. 1st induction followed by test shocks of 5, 10, 20, 30 J; 2nd and 3rd inductions 3 defibrillation attempts incrementing upward from above the highest failed defibrillation on the previous induction. Defibrillation threshold defined as successful test shocks following final induction. *Results:* Defibrillation thresholds were 1st binary search 12.1 ± 4.1J, 2nd binary search 12.4 ± 4.6J, 1st novel protocol 13.0 ± 5.3J, 2nd novel protocol 11.6 ± 3.5J. Correlations; 1st novel protocol vs. 1st binary search α 0.85, p 0.0035. 1st vs. 2nd binary search α 0.92, $p<0.001$. 1st vs. 2nd novel protocol α 0.80, $p=0.0082$. Time in ventricular

fibrillation (90.0 vs. 39.6s), inductions (8.3 vs. 3.1), number test shocks (12.3 vs. 6.6) and total defibrillation energy administration (220 vs. 76.3J) were all higher in the binary search algorithm (all $p<0.01$). *Conclusion:* the novel protocol derives a reproducible defibrillation threshold of similar value to the binary search with substantially reduced ventricular fibrillation time, inductions, therapies and total energy administration.

3.4.2 Introduction

The ideal method for assessing defibrillation threshold would give a precise value (one J resolution) with an accuracy and repeatability to justify this. It would be quick to perform with a low number of fibrillation inductions and defibrillation attempts and a low total fibrillation time. In clinical studies it would be performed through the device being implanted without significant loss of battery life. It would equate to between ED_{75} and ED_{99}.

There is no single accepted method for assessment of defibrillation threshold indicating that a method conforming to these ideals does not exist. All available algorithms are a compromise between accuracy and feasibility.

3.4.3 Aims

To assess the reproducibility of the binary search algorithm

To assess the reproducibility of a novel defibrillation threshold determination algorithm

To compare the time spent in ventricular fibrillation, number of inductions and therapies between the algorithms.

3.4.4 Methods

Seven female pigs, weight 39.7 ± 1.9 Kg, were prepared and anaesthetised as described previously. A dual coil defibrillation lead was deployed with coils positioned in right ventricular apex and superior vena cava. An active housing was implanted subcutaneously in the left pectoral region.

A total of four defibrillation threshold determinations were performed on each animal: two three reversal binary search algorithms as described previously and two by a novel method, figure 3.12↵. The order of algorithms was alternated and the first to be tested was random. In addition to defibrillation threshold time in fibrillation, number of fibrillation inductions and defibrillation therapies and total energy administration were recorded. As a secondary endpoint the values obtained from truncated binary search and version of the novel protocol were examined for repeatability and equivalence. *Statistical analysis*: The repeatability of each method was assessed by calculation of an intra-class correlation coefficient (α). The equivalence of the three reversal binary search and the novel protocol was assessed by performance of an intra-class correlation coefficient between the values obtained on the first assessment of each. A two sided p value of 0.05 or less was considered significant. The accuracy of both methods was assessed by dividing the variability (difference between values) by the mean to give a percentage variability.

Comparisons between algorithms used only the first acquisition of each to avoid artificially inflating the sample size and statistical significance.

3.4.5 Results

Defibrillation thresholds as assessed by the techniques are shown figure 3.13↵.

The binary search was repeatable α 0.951 (95% CI 0.762-0.993) p=0.0006.

The novel protocol was also repeatable α 0.891 (95% CI 0.363-0.981) p=0.0082.

The intra class correlation between the first novel protocol and the first binary search was high indicating that defibrillation thresholds obtained by the two methods are comparable α 0.921 (95% CI 0.539-0.9864) p 0.0035. This was confirmed in by correlating the second assessments of each method α 0.942 (95% CI 0.661-0.990) p 0.0015.

The Bland and Altman analysis showed the novel protocol to give a DFT value of –4.1 to +7.1 J. The binary search has a resolution of -3.8 to +3.1 J.

Comparing the first assessment of each algorithm the novel protocol entailed 56% less time in fibrillation ($p<0.001$), 62% less inductions ($p<0.001$), 47% less defibrillation attempts ($p=0.003$) and 65% less total energy administration ($p<0.001$), figure 3.15.

3.4.6 Discussion

In considering the attributes of an ideal defibrillation threshold assessment algorithm the binary search has an advantage in precision (half increment thresholds can be assigned) and tends to have an advantage in accuracy. The novel protocol reduces, to a statistically and clinically significant degree, time in fibrillation, number of inductions number of therapies and total energy administration.

Adoption of the novel protocol for defibrillation threshold assessment would have potential advantages for both animal and clinical studies.

In animal studies the reduced fibrillation time, inductions, defibrillation attempts and total energy would allow more configurations to be studied in each animal before results became affected by the physiological impact of procedure time, fibrillation time and energy administration. It would also be possible to design more accurate and precise algorithms with repetitions of final inductions or hybrid algorithms with a limited induction search followed by a binary determination.

In human studies full binary searches with multiple reversals are not justifiable due to the risk of end organ damage due to fibrillation time and defibrillation attempts. The comparison in humans should therefore be made between a limited (three or four) induction binary search and the novel protocol. This comparison is possible from the data available because the initial determination of entry point onto the final binary search pathway is equivalent to a limited binary search as used in clinical studies. It is also

possible to examine the usefulness of a truncated two induction version of the novel protocol.

The novel protocol has greater precision than the limited binary search and the results of this study suggest that this is likely to be justified by it tending to have greater accuracy (lower variability) than the limited binary search. It does not appear to have any great advantage in fibrillation time or inductions, nor defibrillation attempts or energy so a fuller validation in humans is required to establish its accuracy compared to a limited binary search.

The truncated novel protocol with two inductions does not appear to have any merit, it has low repeatability and does not represent a great improvement in other parameters over either the full novel protocol or the limited binary search.

If confirmed in humans the novel protocol offers for the first time the possibility of a high resolution defibrillation threshold in clinical studies. This will allow smaller sample sizes aiding research involving defibrillation threshold. Mean total times in ventricular fibrillation of 40 seconds with individual periods of fibrillation almost all under 30 seconds would appear to represent a protocol ethical to repeat twice in a human subject allowing two configurations to be compared. The total energy administration of 76 ± 34 J is also acceptable in terms of the drain on the devices battery.

It should be noted that an accurate and repeatable surrogate of defibrillation threshold is validated in the form of the upper limit of vulnerability. This measure is a surrogate, rather than direct measurement, of defibrillation threshold. It involves multiple shock therapies and a number of ventricular fibrillation inductions. It does not therefore share the advantages of the novel protocol in these regards.

There are a number refinements to the protocol which would make it more suitable to its application. In higher defibrillation thresholds the number of tests shocks should be limited to two before a rescue therapy is administered to avoid prolonged times in ventricular

fibrillation. For human studies in which total time in fibrillation is a major factor in the potential acceptability of a protocol a further two amendments may be made. (i) If a rescue therapy is required following the second induction and the second induction protocol is repeated in the therapy ladder above then the successful therapy of this induction would be regarded as the defibrillation threshold ad the third induction therapy ladder omitted. (ii) If a rescue therapy is required in the final induction the second induction may be repeated and started an increment above the last failed test shock. The defibrillation threshold would then be taken as the successful therapy in this induction. *Limitations of the study*: thus far the protocol has been attempted on only seven animals. This has provided sufficient data to validate the protocol for animal use in future therapies but human studies are required to validate the algorithm in clinical research. The protocols acceptability decreases with increasing defibrillation threshold and the amendments tested above require validation. The tendency of the novel protocol to be more accurate than the limited binary search requires proof in study with larger numbers, ideally in humans.

3.4.7 Conclusion

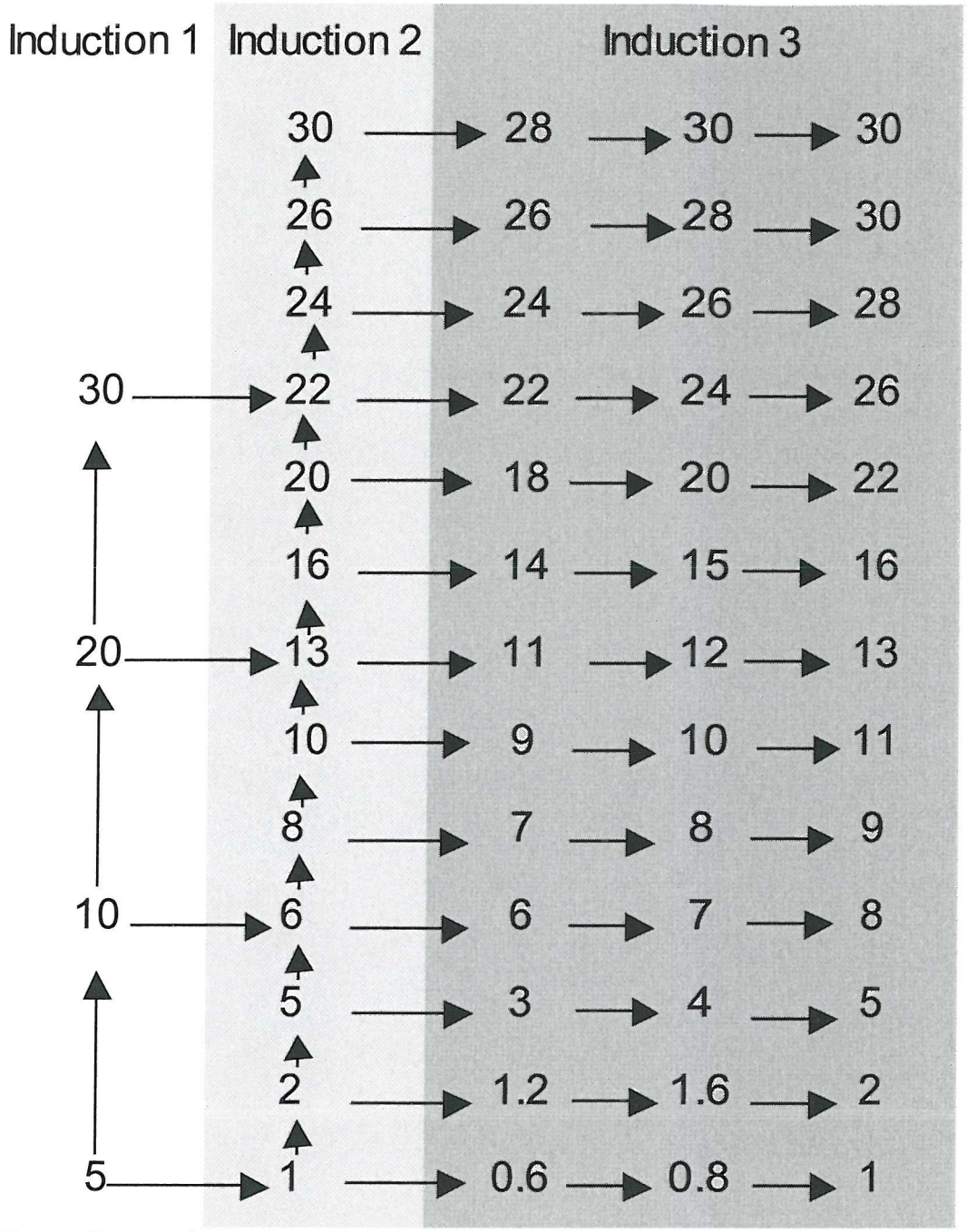
A three-induction defibrillation threshold determination algorithm is repeatable and reduces fibrillation time and inductions as well as defibrillation attempts and total energy compared to a three reversal binary search.

The defibrillation threshold values obtained by the three-induction algorithm and the three reversal binary search are equivalent.

This algorithm is potentially more accurate than a limited binary search with similar fibrillation and defibrillation parameters.

A truncated two-induction protocol lacks repeatability.

Figure 3-12 Three-induction Defibrillation Threshold Determination Algorithm;



Wessex Protocol

Test therapies are shown in Joules, a failed sequence would be followed by a 30 Joule rescue shock. The Induction would then be repeated and a further three test therapies administered an increment point above the last failed shock on the same therapy ladder.

Figure 3-13 Comparison DFT Determination algorithms

	Full Binary	3 Induction	Limited Binary	2 Induction
Defibrillation threshold, J	12.1+/-4.1	13.0+/-5.3	13.1+/-6.4	13.9+/-5.4
Fibrillation time, s	90+/-20	40+/-11	44.3+/-11.4	33.6+/-12.0
Fibrillation inductions	8.3+/-1.7	3.1+/-0.4	4.3+/-0.76	2.9+/-1.2
Defibrillation attempts	12.3+/-1.7	6.6+/-1.3	5.4+/-1.0	5.0+/-1.9
Total Energy Administered, J	220+/-52.0	76.3+/-34.4	106+/-36.3	70.3+/-40.7
Repeatability %	11+/-9	18+/-12	25+/-36	36+/-26
Intra Class Correlation,	0.99	0.89	0.9	0.5
P (<0.05=significant)	0.0006	0.008	0.0069	0.1

3.5 Repeatability of a refined limited induction defibrillation threshold compared with limited binary search

3.5.1 Abstract

Introduction: Ventricular defibrillation threshold assessment in clinical studies is usually limited by the ethical requirement to limit the number of ventricular fibrillation inductions. Binary searches are the gold standard. A greater the number of reversal points ensures a increasingly accurate/repeatable defibrillation threshold. Each point requires a fibrillation induction. Binary searches are commonly limited to 3 points in clinical studies. We refined the previously described novel method for DFT assessment and compared it to a three reversal binary search.

Methods: 10 pigs were anesthetized and implanted with a left pre-pectoral ICD (Medtronic Marquis 7274), RV and SVC defibrillation leads (Medtronic 6942 and 6937). Defibrillation thresholds were alternately assessed by 3-point binary search and refined protocol. Each protocol was repeated 3 times. The defibrillation sequences were: Binary Search-three inductions each followed by a test shock either above or below the previous test shock as determined by it success or failure, the defibrillation threshold taken as the lowest successful test shock. Refined protocol -three inductions each followed by a series of 3 escalating test shocks. The first induction test shocks were 5,10 and 20 J. The second and third induction test shocks incremented from just above the highest failed test shocks of the prior induction, the defibrillation threshold taken as the successful test shock after the third induction. The repeatability of the protocols was expressed as a variability by comparing the range of defibrillation thresholds with the mean defibrillation threshold for each protocol in each pig.

Results: The variability of the refined protocol (29 ± 35%) was superior to Binary search (75 ± 16%) p=0.001. The refined protocol required similar fibrillation times (35.6 vs.

35.1s, p>0.05), less energy administration (81.5 vs. 97.2 J, p=0.001) and gave almost identical mean defibrillation threshold results (16.3 vs. 16.3 J, p>0.05) to the binary search. Conclusion: The refined protocol is able to measure a highly repeatable defibrillation threshold with significantly less energy administration than a 3 reversal binary search. This refined novel protocol may be considered the gold standard means of determining defibrillation threshold in clinical studies.

3.5.2 Introduction

The concept of defibrillation threshold is flawed as there is no single value either side of which therapies may be dichotomised on the basis of success or failure, rather defibrillation outcome is probabilistic, the chance of success increasing with energy describing a sigmoid curve. The value given to defibrillation threshold is therefore as much a refection of the method of estimation as it is the implanted system or substrate. Differing methods of estimation will give defibrillation threshold values equivalent to varying points on the curve relating to the chance of defibrillation success (EDx where x is the % chance of success of that therapy).

The ideal method for assessing defibrillation threshold would give a precise value (one J resolution) with a repeatability to justify its resolution. It would be quick to perform with a low number of fibrillation inductions and defibrillation attempts and a low total fibrillation time. In clinical studies it would be performed through the device being implanted without significant loss of battery life. It would equate to between ED_{75} and ED_{99}.

There is no single accepted method for assessment of defibrillation threshold indicating that a method conforming to these ideals does not exist: all available algorithms are a compromise between accuracy and feasibility. There are several methodologies available for estimating defibrillation threshold, step up protocols, step down protocols and binary searches.

Step up protocols, in which therapies of progressively increasing strength are administered until a successful attempt occurs will tend to give a value equivalent to ED25-50. Step down protocols administer progressively lower therapies until a failure occurs and tend to equate to ED70. Both of these types of protocol are highly susceptible to bias by outlier results. Binary search protocols start from a predefined midpoint and the result of each therapy determines whether the following therapy is increased or decreased in strength. Binary searches give results equivalent to an EDx between step up and step down protocols but more importantly are less susceptible to outlier results and therefore have greater repeatability, for this reason they are considered the gold standard in the assessment of DFT. Binary searches are dependant on the number of reversals for their accuracy and resolution, because each reversal requires a fibrillation induction the accuracy of the protocol is limited in human studies by the number of inductions that may safely be performed. Binary searches in humans are commonly limited to three inductions severely limiting their repeatability. In the previous chapter I described a pilot study of a limited induction, multiple test shock method for determining defibrillation threshold. This protocol showed promise but had two major limitations: Firstly in individuals with high defibrillation thresholds the protocol did not perform well due to the long fibrillation times creating excessive variation in results. Secondly outlier low results in the first therapy ladder led to an excessive number of fibrillation inductions. For use in clinical studies precise defibrillation threshold are only required up to 20 J as above this level a system revision is required. This fact was used to redesign the protocol as described below to focus on the clinically useful range of defibrillation threshold measurements. Statistical analysis was also altered for this protocol to reflect percentage as opposed to numerical variability.

3.5.3 Aims

To compare a refined novel protocol for the assessment of defibrillation threshold with a binary search protocol.

3.5.4 Methods

. Ten female pigs, weight 41.7 ± 1.4 Kg were anaesthetised and monitored as previously described.

Defibrillation system configuration: single coil defibrillation leads (Medtronic 6943 and 6937) were advanced to RV apex and SVC. An implantable defibrillator (ICD) was inserted subcutaneously in the left pectoral area (Medtronic 7274). Induction of fibrillation was by 5s 50Hz AC current application.

Defibrillation threshold determination-binary search: see figure 3.14↵. The binary search requires three VF inductions, the device is programmed to detect and defibrillate at the strength appropriate to the point on the algorithm. Should the animal remain in fibrillation the device is programmed to deliver a 30 J rescue therapy. The DFT is lowest successful defibrillation attempt, a failure at 20 J was regarded as a DFT of 30 J assuming the majority of 30 J rescue shocks had been successful.

Defibrillation threshold determination-Refined protocol: Figure 3.15↵. The refined protocol also requires three inductions but after each induction the device is programmed to deliver up to three test shocks of escalating value followed if necessary by a 30 J rescue shock. The first induction is followed by test shocks of 5, 10 and 20 J. The second and third inductions are followed by test shocks escalating from just above the highest failed defibrillation therapy of the previous induction. The DFT is the successful test shock on the third induction. Any one failure at 20 J was regarded as a DFT of 30 J assuming the majority of 30 J rescue shocks had been successful.

Should no therapies in the second induction be successful the third induction would be followed by up to three test shocks from the second induction therapy ladder an increment

above the failed therapy, the successful therapy would be regarded as DFT (resolution sacrificed but inductions limited).

Should all third induction test shocks fail after a successful second induction test shock the DFT would be the lowest successful test shock from previous inductions which had not subsequently failed. If all successful test shocks had subsequently failed a fourth induction would be required using the third induction therapy ladder an increment above the highest failed test shock.

Technical considerations: this protocol is made possible by the programmability of the Medtronic 7274 device which allows independent programming of defibrillation attempts in the therapy screen. It does not however allow three defibrillation therapies under 10 J, a difficulty if a success at 5 J occurs in the first induction. This may be overcome by pre-programming the first two therapies and all subsequent therapies disabled. The manual defibrillation therapy in the EP study screen is set to the third test shock strength to allow ease of delivery if required.

Pigs have high amplitude T wave resulting in the potential of rate being sensed at twice the actual rate and VF over detection. Device programming was as follows:

Brady therapies: ODO

Detection: VF Enabled, Initial detection 18/24, redetection 9/12, interval 240 ms (250 bpm). FVT and VT zones off.

Sensitivity: Ventricular 1.2 mV (Atrial port plugged)

VF Therapies: test therapies set to protocol requirements followed by 30 J rescue shock, all AX>B, remaining therapies off.

Statistical analysis: in each animal a total of six DFT determinations, three of each protocol, were performed alternating the refined protocol and the binary search. The number of inductions and shocks, total energy administration, time in VF and DFT were measured for each protocol. The within subject variability of each protocol was compared

by expressing the difference between maximum and minimum DFT values as a percentage of the mean average of the three repetitions of the protocol in that animal. The DFT variability and other parameters were compared between protocols using a paired T test, a two sided p value of >0.05 was considered significant.

3.5.5 Results

The differences between the two methods are shown in figure 3.16.

There is significantly less variability in the Refined protocol (29 ± 35%) than the binary search (75 ± 16%) p=0.001. The Refined protocol required similar VF times (35.6 vs. 35.1s, p>0.05), less energy administration (81.5 vs. 97.2 J, p=0.001) and gave almost identical mean DFT results (16.3 vs. 16.3 J, p>0.05) to the binary search, the correlation between the protocols was, however, weak, figure 3.17, r=0.53.

3.5.6 Discussion

Should this protocol be validated in humans the ability to determine accurate DFTs would dramatically reduce the number of patients required in clinical trials comparing this parameter. The VF times and total energy administration are even low enough that this algorithm may be regarded as an acceptable alternative to safety margin testing in clinical practice, this would allow large centres to build up registries of accurate DFT results establishing baseline data for prospective and future retrospective studies.

The repeatability of the protocol stems from its combination of step up (between test shocks within an induction) and step down (between inductions) nature and multiple increments. The number of increments and provision for additional steps prevent an outlier result from grossly distorting the final result.

Limitations of the Study This work was performed in animals, validation in humans is required before its findings can be applied to clinical practice. The study was made possible by the programmability and fast charge times of the device used, whether the same results would be possible with other devices is unclear.

3.5.7 Conclusions

A protocol for determining DFT based on multiple test shocks after each induction is more accurate and requires less total energy administration than a three reversal binary search.

Figure 3-14 Binary Search Algorithm

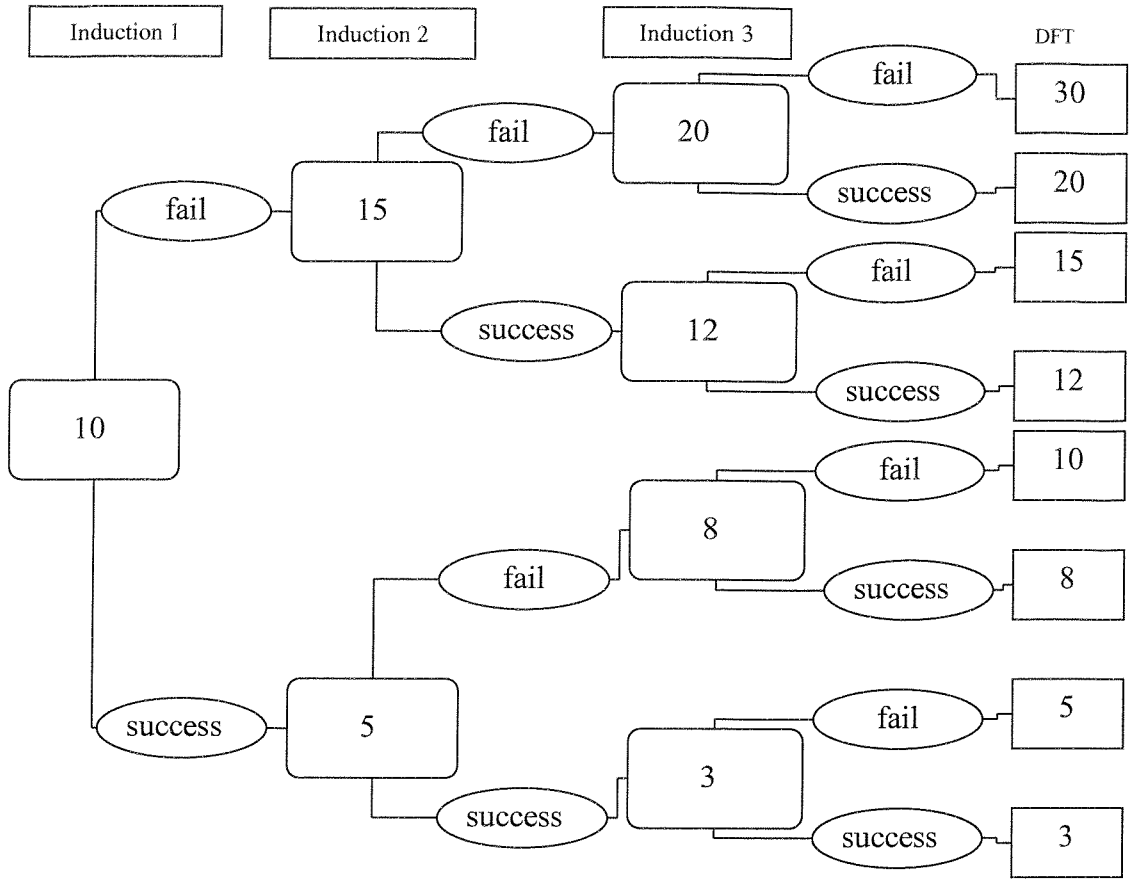
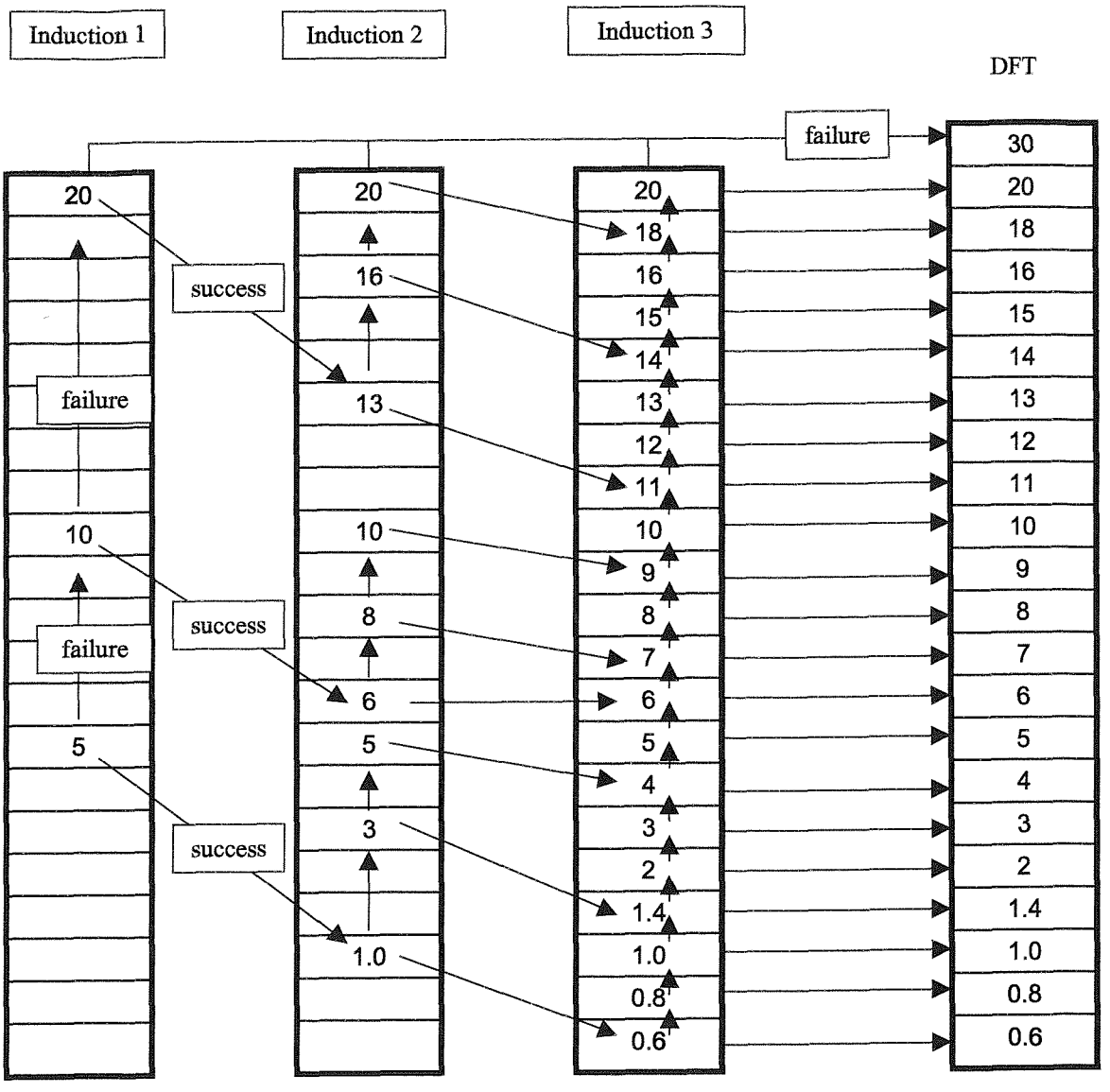


Figure 3-15 Wessex Protocol Algorithm

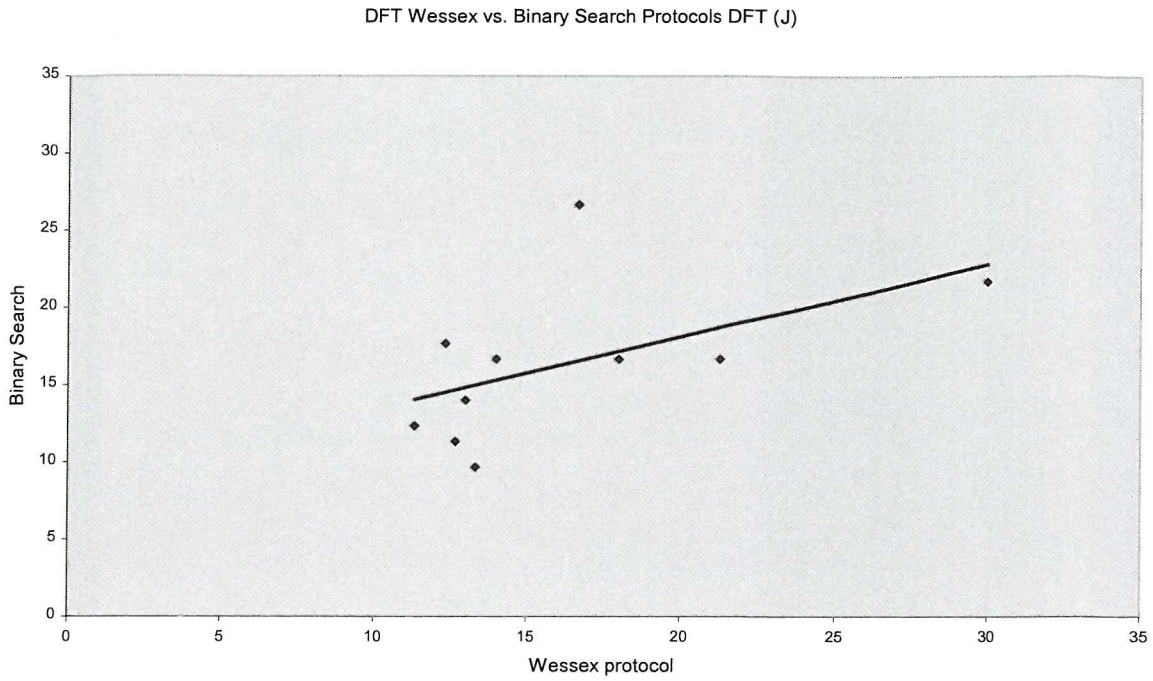


↵

Figure 3-16 Wessex vs. Binary Search Protocol Results

	Binary Search	Limited Induction	Significance
DFT (J)	16.3 ± 6.6	16.3 ± 6.6	0.96
Range (J)	8.6 ± 6.0	5.0 ± 6.8	0.29
Variability (%)	75.2 ± 16.1	28.8 ± 34.7	<0.01
Fibrillation time (s)	36.1 ± 7.2	35.7 ± 10.1	0.86
Inductions (n)	3 ± 0	2.7 ± 0.8	0.06
Shocks (n)	5.0 ± 6.4	6.0 ± 1.6	<0.01
Total Energy (J)	97.2 ± 22.1	81.5 ± 22.5	<0.01

Figure 3-17 Defibrillations Thresholds



4 HUMAN CORONARY VENOUS PACING AND DEFIBRILLATION

4.1 Sole Anodal Middle Cardiac Vein Defibrillation in Man

4.1.1 Abstract

Introduction: auxiliary coronary venous shocks in defibrillation therapy have been shown to decrease defibrillation threshold. It has not previously been shown that coronary venous defibrillation without a right ventricular component is an effective configuration for defibrillation in man. *Aims:* to compare right ventricular and middle cardiac vein defibrillation in man. *Methods:* eight patients (7 m) aged 51.8 ± 12.7 met NASPE criteria for defibrillator implantation. RV/SVC and middle cardiac vein (ELA medical) defibrillation electrodes were placed transvenously. An emulator can was implanted in the left pectoral region. Defibrillation thresholds were measured using a binary search, for the following configurations: MCV → SVC + Can and RV → SVC + Can. *Results:* middle cardiac vein lead placement was possible in five out of eight patients. In one patient middle cardiac vein was short, in one middle cardiac vein could not be selectively catheterised, in one coronary sinus was not catheterised. Total screening time for procedure was 16.3 ± 7.4 minutes: screening time from catheter engaging middle cardiac vein to final lead position was 1.1 ± 0.7 minutes. Defibrillation threshold (J) were RV 8.8 ± 3.2 vs. middle cardiac vein 10.0 ± 5.6 (p=0.587) and impedances (Ω) RV 39.2 ± 3.1 vs. middle cardiac vein 56.6 ± 9.7, (p=0.007). *Conclusion*: The middle cardiac vein is an effective site for defibrillation coil placement in acute circumstances. This justifies further research toward entirely transvenous systems: pacing, resynchronisation and defibrillation may be possible without crossing any heart valves.

4.1.2 Introduction

Transvenous defibrillation with implantable cardioverter defibrillators has been an established therapy for primary and secondary prevention of life threatening ventricular arrhythmias for several years(19;20;22-24).

We have previously demonstrated in a porcine model that it is possible to significantly reduce defibrillation requirements if a lead is placed transvenously in the coronary venous system(53-55;106) and that single capacitance auxiliary shocks from middle cardiac vein are effective and safe in acute human defibrillation(103).

It has not previously been shown that coronary venous defibrillation may be an alternative rather than an adjunct to endocardial configurations.

4.1.3 Aims

To compare RV endocardial and middle cardiac vein anodal defibrillation in humans

4.1.4 Methods

This was a prospective study of eight patients (one female; aged 51.8 ± 12.7 years) undergoing implantation of a defibrillator for NASPE/BPEG indications. The indications for defibrillator implantation were secondary prevention in six and primary prevention in two, four patients had non-ischaemic dilated cardiomyopathy, two ischaemic left ventricular impairment and two repolarisation disorders, Figure 4.1↵.

Devices were implanted using local anaesthesia and sedation with midazolam. A dual coil defibrillation lead was placed transvenously in the right ventricular apex via the left subclavian vein. The proximal coil was positioned in the superior vena cava. Standard pacing/sensing characteristics were assessed and the leads repositioned if unsatisfactory. The middle cardiac vein was then cannulated from the left subclavian vein using an 8Fr multipurpose angiographic catheter. Venography was performed in right anterior oblique (RAO), and left anterior oblique (LAO) projections. A custom designed over the wire

polyurethane insulated electrode with a 4.4 Fr Platinum-Iridium alloy (80/20) 55 mm 334 mm^2 unipolar defibrillation coil (Swift OTW, Ela SA, Fr) was then advanced to the distal middle cardiac vein Figure 4.2;4.3↵. An active can emulator was inserted subpectorally on the left side. Screening times for procedure and vein cannulation to lead deployment intervals were recorded. Defibrillation threshold testing was then performed using the following electrode configurations in random order: RV→SVC + Can and middle cardiac vein→SVC + Can, with the RV/middle cardiac vein designated as the anode. Ventricular fibrillation induction and defibrillation threshold testing was performed as described previously. After defibrillation testing, the middle cardiac vein electrode was removed and the defibrillator implanted in the standard manner. *Statistical Analysis:* Results are given as mean ± SD. Defibrillation thresholds and impedances were compared using a paired T test, a two tailed p value of 0.05 or less considered significant.

4.1.5 Results

Lead placement was possible in five patients. In one patient it was not possible to catheterise coronary sinus, in one middle cardiac vein was a vestigial remnant and in one middle cardiac vein could not be selectively catheterised. Total screening times for procedure were 16.3 ± 7.4 minutes, time from engaging middle cardiac vein to final lead position was 1.1 ± 0.7 minutes. No adverse incidents were observed in any patient.

There was no difference defibrillation threshold (RV 8.8 ± 3.2 vs. Middle cardiac vein 10.0 ± 5.6, p=0.58) between the configurations. Impedances were (RV 39.2 ± 3.1 vs. middle cardiac vein 56.6 ± 9.7, p=0.007). Despite the higher impedance in the middle cardiac vein configuration defibrillation thresholds by calculated mean current did not significantly differ (RV 0.47 ± 0.1 vs. Middle cardiac vein 0.41 ± 0.12, p=0.20).

Individual defibrillation threshold, current, and impedance measurements are shown, Figure 4.4↵.

4.1.6 Discussion

This is the first randomised controlled trial to demonstrate the feasibility of non-endocardial transvenous defibrillation in man. Furthermore the site used is a tributary of coronary sinus, a structure in current clinical use for pacing therapies (cardiac resynchronisation and anti tachycardia pacing) that are routinely functions of defibrillators. In this study parity with, rather than superiority over, RV endocardial defibrillation has been demonstrated.

Previous human studies of coronary venous defibrillation have demonstrated reduction in DFT by current (through middle cardiac v;ein(103)) or by energy (through lateral cardiac vein(101;102)) but have used auxiliary shocks maintaining an RV endocardial coil in the configuration. We have shown that placement of defibrillation electrodes in the middle cardiac vein is possible in man and the defibrillation threshold is similar for RV and middle cardiac vein anodes when defibrillating to a SVC + AH cathode.

Advantages of non-endocardial defibrillation beyond the potential for defibrillation threshold reduction exist as such systems have no requirement to traverse tricuspid valve. This raises the possibility of being implantable in patients with prosthetic tricuspid valves or morphologically abnormal RVs: the latter a group at high risk of life threatening ventricular arrhythmia(32) but who may currently require thoracotomy to implant defibrillators.

In this acute human study the feasibility of non-endocardial, transvenous defibrillation has been demonstrated at a similar defibrillation threshold to conventional configurations. Once placed the electrode maintained a stable position for the duration of this acute study aided by the proximal tortuosity of the vessel.

Limitations Of The Study: in human studies accuracy of defibrillation threshold determination and number of configurations that can be tested are limited by the number of VF inductions it is ethical to perform. Numbers in this study are small and it is not

powered to detect small differences in defibrillation threshold however a near equivalence between configurations has been demonstrated.

The impedance of the MCV lead was significantly higher than the RV lead therefore even if defibrillation requirements by current had been reduced by MCV defibrillation this may not have been reflected in the defibrillation energy requirements.

Neither this nor any other published animal or human work have assessed long term stability or safety of MCV defibrillation electrodes.

4.1.7 Conclusion

Placement of defibrillation electrodes in the middle cardiac vein is possible in man and the defibrillation threshold is similar for RV and MCV anodes when defibrillating to a SVC + AH cathode.

It is possible that defibrillation, anti bradycardia pacing, anti-tachycardia pacing and cardiac resynchronisation therapy may all be delivered by a single, transvenous, non endocardial lead.

Figure 4-1 Patient characteristics

Patient	Gender	Age	Weight (Kg)	Aetiology	Indication	Inducible	Amiodarone	EF	NYHA Class
1	Male	72	106	IHD	MVT	Yes	No	0.30	1
2	Male	54	82	IHD	MVT	Yes	No	0.31	1
3	Male	55	87	DCM	MVT	Not done	Yes	0.30	2
4	Male	67	80	DCM	MVT	Yes	No	0.30	2
5	Female	39	100	RD	Primary	Not done	No	0.55	1
6	Male	37	114	RD	Primary	Not done	No	0.55	1
7	Male	43	78	DCM	MVT	Not done	No	0.45	1
8	Male	47	107	DCM	MVT	Yes	No	0.28	2

IHD: ischaemic heart disease, DCM: dilated cardiomyopathy, RD: repolarisation disorder, MVT: monomorphic VT, primary: primary prevention, NYHA: New York Heart association.

↵

Figure 4-2 MCV lead in place, LAO

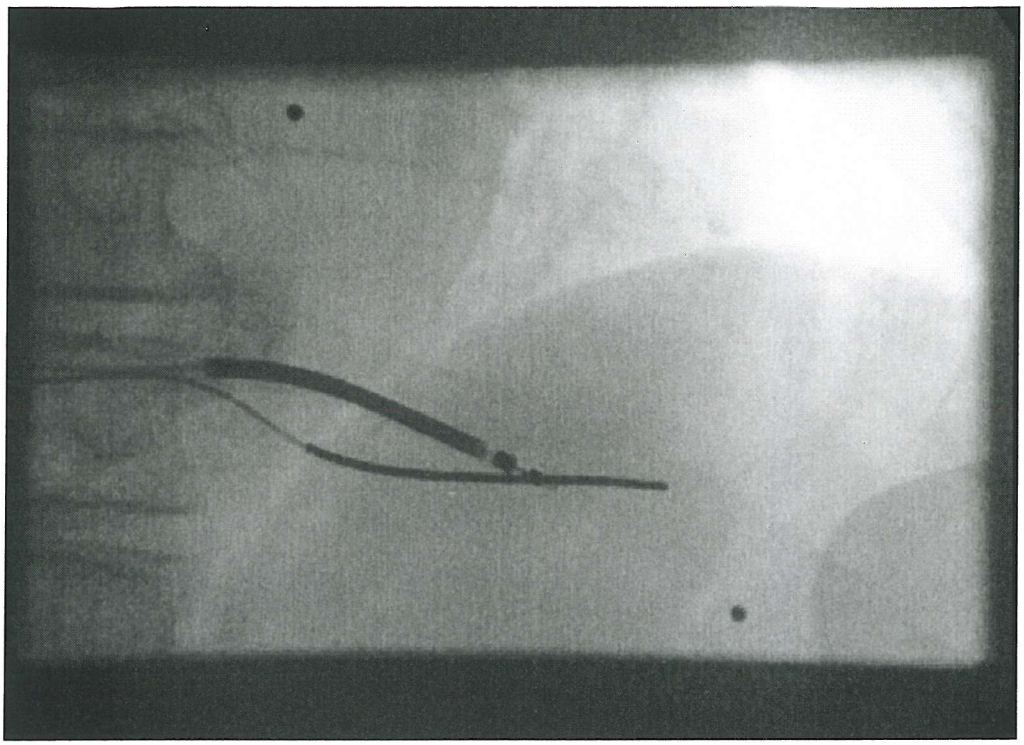
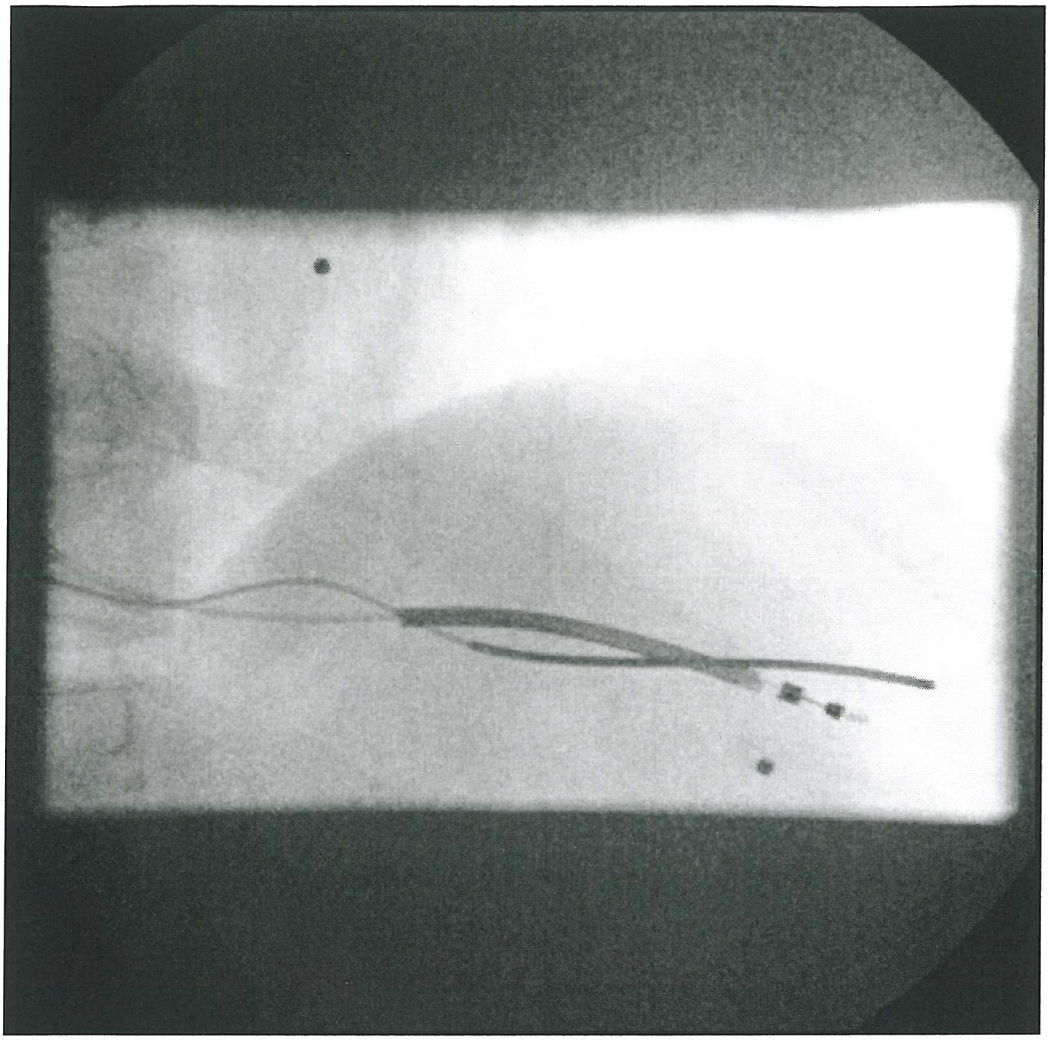


Figure 4-3 MCV lead in place, RAO



GILBERT, David
SGH Rm17
3494087
15/07/1935
Dr J M Morgan

Hicor DCM
04/10/2002 15:13:28
RAO: 23. CRAN: 11. [Plane A]
Scene: 4
Frame: 2

Figure 4-4 Defibrillation Characteristics

Patient	Active Housing	Pulse Generator	RV/SVC Coil	Defibrillation threshold		Impedance (Ω)	
				RV	MCV	RV	MCV
1	Ela 614	MTR 5358	GDT 0148	13	13	36	51
2	CS not cannulated						
3	MCV Vestigial						
4	Ela 614	MTR 5358	MTR 6947	4	4	40	50
5	GDT 1870	GDT 1870	GDT 0148	9	18	37	58
6	MCV not cannulated						
7	MTR 7274	MTR 7274	GDT 0148	9	9	39	51
8	Ela 614	Ela 614	GDT 0148	9	6	44	73

RV: Right ventricle, SVC: Superior Vena Cava, Ela: Ela medical, GDT: Guidant, MTR: Medtronic, MCV: middle cardiac vein, CS: coronary sinus

4.2 Auxiliary Lateral Cardiac Vein Defibrillation in Man

4.2.1 Abstract

Introduction: auxiliary lateral coronary venous shocks in defibrillation therapy have been shown to decrease defibrillation threshold in animal studies. Similar studies in man have required dual capacitance socks limiting the utility of the technology. *Aims:* to compare standard right ventricular and auxiliary lateral coronary plus right ventricular defibrillation in man. *Methods:* Four patients, all male aged 64 ± 10 years met NASPE criteria for defibrillator implantation. RV/SVC and lateral cardiac vein (ELA medical) defibrillation electrodes were placed transvenously. An emulator can was implanted in the left pectoral region. Defibrillation thresholds were measured using a binary search, for the following configurations: RV → SVC + Can and RV + LCV → SVC + Can. *Results:* Lateral cardiac vein electrode placement was possible in all patients. Total screening time for procedure was 9.4 ± 0.9 minutes: screening time from lead introduction to final position was 3.5 ± 2.2 minutes. Defibrillation threshold (J) were RV 10.2 ± 2.9 vs. RV + LCV 16.0 ± 9.7 (p=0.36) and impedances (Ω) RV 44.5 ± 4.6 vs. RV + LCV 38.5 ± 4.6, (p=0.16). *Conclusion*: Without dedicated defibrillation circuitry lateral cardiac vein lacks clinical utility as a site for auxiliary defibrillation.

4.2.2 Introduction

Auxiliary lateral coronary venous defibrillation has attracted previous interest due to its potential to improve defibrillation efficacy and potential combined functionality with resynchronisation pacing electrodes. Prior studies on this topic have required dedicated circuitry to control the proportion and timing of the auxiliary shock(101;102;105;107). As previously demonstrated in this thesis we have an electrode effective as a sole anode in defibrillation. We sought to investigate the utility of this electrode in auxiliary lateral vein defibrillation without dedicated circuitry to distribute current.

4.2.3 Aims

To compare sole anodal RV endocardial and simultaneous RV and auxiliary lateral cardiac vein defibrillation in humans.

4.2.4 Methods

This was a prospective study of four patients (four male; aged 64± 10 years) undergoing implantation of a defibrillator for NASPE/BPEG indications. The indications for defibrillator implantation were monomorphic ventricular tachycardia in two, ventricular fibrillation in one and primary prevention in one. All patients had ischaemic heart disease, Figure 4.5↵.

Devices were implanted using local anaesthesia and sedation with midazolam. A dual coil defibrillation lead was placed transvenously in the right ventricular apex via the left subclavian vein. The proximal coil was positioned in the superior vena cava. Standard pacing/sensing characteristics were assessed and the leads repositioned if unsatisfactory. The coronary sinus was then cannulated from the left subclavian vein using an 8Fr multipurpose angiographic catheter. Venography was performed in right anterior oblique (RAO), and left anterior oblique (LAO) projections. A custom designed over the wire polyurethane insulated electrode with a 4.4 Fr Platinum-Iridium alloy (80/20) 55 mm 334

mm^2 unipolar defibrillation coil (Swift OTW, Ela SA, Fr) was then advanced into a lateral cardiac vein Figure 4.6;4.7↵. An active can emulator was inserted subpectorally on the left side. Screening times for procedure and vein cannulation to lead deployment intervals were recorded. Defibrillation threshold testing was then performed using the following electrode configurations in random order: RV→SVC + Can and RV + LCV→SVC + Can, with the RV/RV+LCV designated as the anode. Ventricular fibrillation induction and defibrillation threshold testing was performed as described previously. After defibrillation testing, the middle cardiac vein electrode was removed and the defibrillator implanted in the standard manner. *Statistical Analysis:* Results are given as mean ± SD. Defibrillation thresholds and impedances were compared using a paired T test, a two tailed p value of 0.05 or less considered significant.

4.2.5 Results

Lead placement was possible in all four patients. Total screening time for procedure was 9.4 ± 0.9 minutes: screening time from lead introduction to final position was 3.5 ± 2.2 minutes. Defibrillation thresholds (J) were RV . SVC + Can 10.2 ± 2.9 vs. RV + LCV . SVC + Can 16.0 ± 9.7 (p=0.36) and impedances (Ω) RV . SVC + Can 44.5 ± 4.6 vs. RV + LCV. SVC + Can 38.5 ± 4.6, (p=0.16).

Individual defibrillation threshold, current, and impedance measurements are shown, Figure 4.8↵.

4.2.6 Discussion

Both the principal of auxiliary left ventricular defibrillation and the efficacy of the electrode used have been previously demonstrated. The novelty in this study arises from the use of an auxiliary electrode without any control exerted over the relative proportion of current passing through the two anodes. Although other studies also controlled the inter shock interval they maintained some benefit with simultaneous shocks(105;107). It is

therefore apparent that the proportion of current diverted into the lateral cardiac vein is an important variable. In other studies approximately 10% of energy was diverted through the coronary venous electrode(101;102;105;107), in this study this proportion is not known and cannot be calculated from the impedances as the shared portion of the circuit appears to have its electrical properties altered by auxiliary defibrillation. As shown by the failed one patient pilot lateral cardiac vein to SVC + Can is not an efficacious route of defibrillation in its own right. The disadvantage of auxiliary shocks used in these studies is the added complexity in the circuitry required to split the shock.

4.2.7 Conclusion

Auxiliary lateral cardiac vein defibrillation without dedicated circuitry to control current distribution between auxiliary and main anodes is not a reliable technique for defibrillation in man.

Figure 4-5 Patient characteristics

Patient	Gender	Age	Weight (Kg)	Aetiology	Indication	Amiodarone
1	Male	52	61	IHD	MVT	No
2	Male	75	69	IHD	MVT	Yes
3	Male	71	81	IHD	VF	No
4	Male	57	114	IHD	Primary	No

IHD: ischaemic heart disease, MVT: monomorphic ventricular tachycardia, primary: primary prevention

↵

Figure 4-6 LCV lead in place, LAO

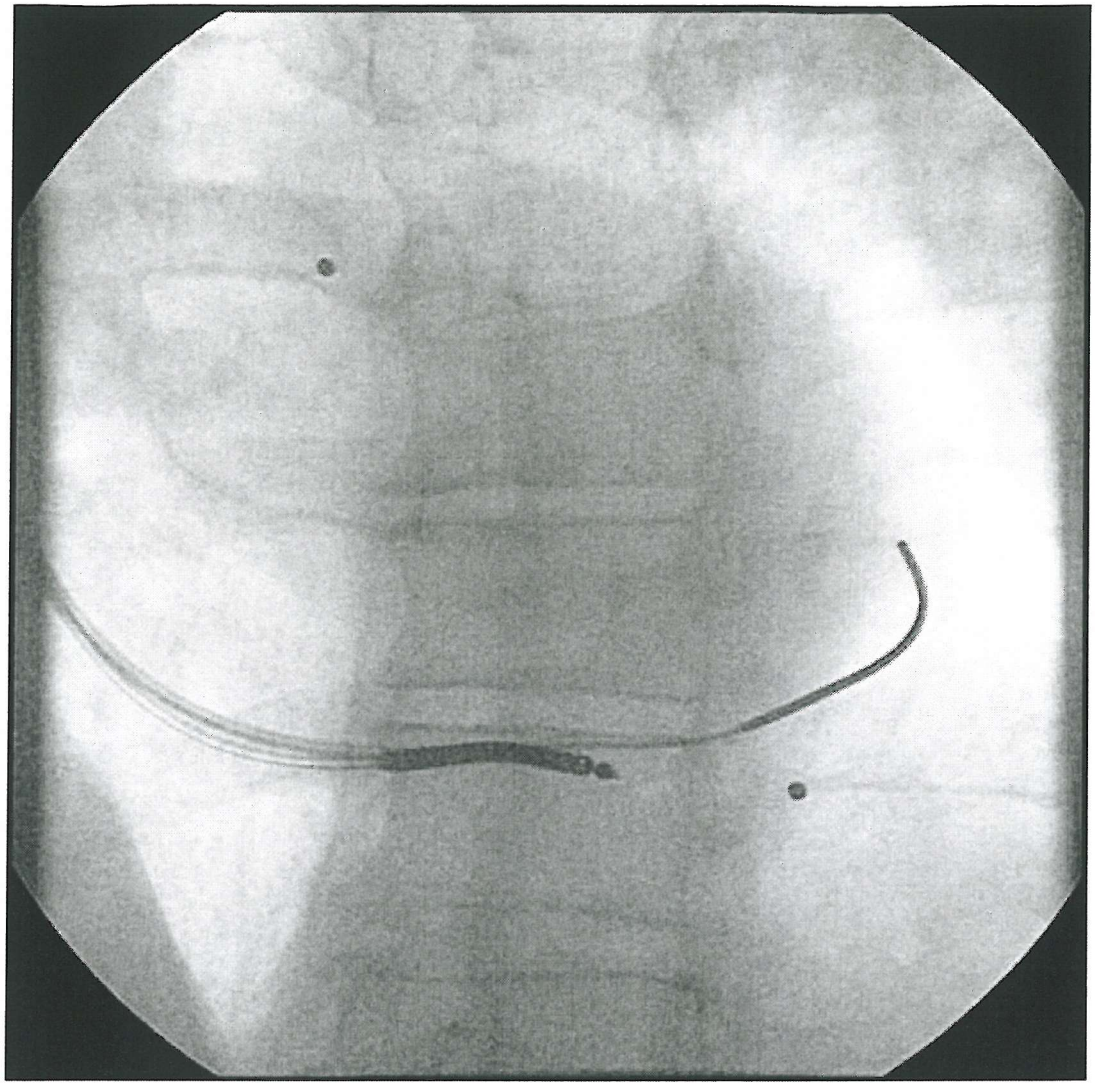
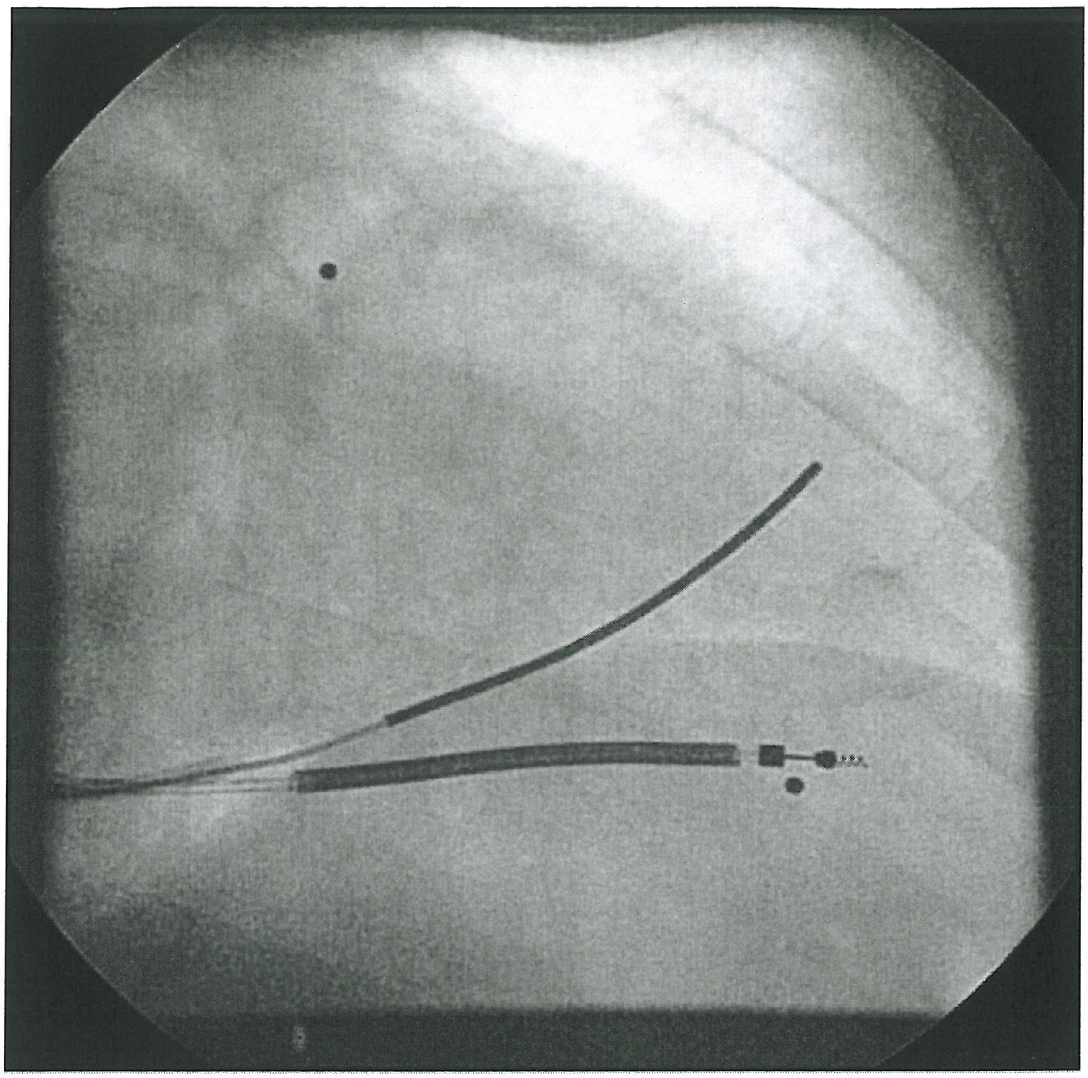


Figure 4-7 LCV lead in place, RAO



↵

Figure 4-8 Defibrillation Characteristics

Patient	Defibrillation threshold		Impedance (Ω)	
	RV	RV+LCV	RV	RV+LCV
1	13	9	39	34
2	6	18	41	34
3	13	6	49	44
4	9	31	49	42

RV: Right ventricle, SVC: Superior Vena Cava, LCV: Lateral cardiac vein

4.3 Development of Resynchronisation Criteria in Defibrillator Recipients

4.3.1 Abstract

Introduction: there is a large crossover area between indications for cardiac resynchronisation therapy and implantable defibrillators. As heart failure symptoms tend to progress over time it may be presumed that a proportion of defibrillator recipients will develop criteria for resynchronisation therapy. *Aims:* to identify the proportion of implantable cardioverter defibrillator recipients progressing to cardiac resynchronisation therapy indications as recognised by ACC/AHA/NASPE over 5 years. To evaluate the impact of baseline conduction disturbance and ventricular function on this proportion. *Methods:* the Wessex defibrillator database was analysed and those individuals followed up for more than five years identified. Proportions and predictors of progression to cardiac resynchronisation therapy criteria were assessed. *Results:* of 60 patients meeting inclusion criteria five progressed to cardiac resynchronisation therapy criteria within five years. All five came from the subset of 14 who had left ventricular ejection fraction (LVEF) under 35% and QRS durations over 130 msec on implantation of their devices *Conclusion:* the overall rate of progression to cardiac resynchronisation therapy criteria is 8% at 60 months. Those patients with LVEF <35% and QRS duration >130 msec have a 36% chance of developing resynchronisation criteria within five years of defibrillator implant. Consideration should be given to implanting resynchronisation capable devices in these patients at the time of initial defibrillator implantation.

4.3.2 Introduction

Current guidelines recommend the use of cardiac resynchronisation therapy (CRT) where ejection fraction (LVEF) is under 35%, QRS duration is over 130 msec and the patients symptoms put them in New York Heart Association (NYHA) class III or IV after appropriate medical therapy(124). These criteria follow scientific scrutiny of cardiac resynchronisation therapy by bi ventricular pacing for moderate to severe congestive heart failure (CHF) with interventricular conduction delay (125-129).

Implantable cardioverter defibrillators (ICD) are established as the treatment of choice for primary(19-21) and secondary(22-24) prevention of life threatening ventricular arrhythmias, particularly in ischaemic heart disease. Application of internationally recognised guidelines(124) for their usage would lead to implantation rates of over 100 per million per year and extension to include the most recent evidence(21) over 200 per million per year(130).

The majority of defibrillator and all cardiac resynchronisation therapy recipients have left ventricular impairment. There is, therefore, a significant overlap in indications for the two devices. Defibrillators capable of delivering cardiac resynchronisation therapy (CRT-ICD) have been commercially available for several years.

CHF and conduction delay are progressive conditions, it is inevitable that a number of individuals implanted with defibrillator will develop cardiac resynchronisation therapy indications during the lifetime of their device. Identification of those most likely to progress would allow the implantation of CRT-ICD in those patients in whom only defibrillators were indicated at the time of insertion. This may represent a cost effective implantation strategy and reduce requirement for further procedures.

We investigated the proportion of defibrillator recipients progressing to cardiac resynchronisation therapy criteria within 60 months of implant and the impact of baseline conduction disturbance and reduced LV function on this proportion.

4.3.3 Aims

To determine the proportion of defibrillator recipients progressing to criteria for resynchronisation pacing within five years of implant.

To determine the impact of baseline conduction disturbance and left ventricular impairment on this proportion

4.3.4 Methods

The Wessex Cardiothoracic Centre was the sole implanting hospital for a population of 3.5 million for the period of the study.

The Wessex defibrillator database has prospectively recorded all defibrillators implanted in this hospital since 1989. Using this source and additional information from medical records we identified patients who progressed to cardiac resynchronisation therapy criteria after device insertion.

Definitions: cardiac resynchronisation therapy criteria were defined as NYHA class III-IV heart failure with LVEF under 35% and QRS duration of 130 msec or more(124).

Inclusion, exclusion and endpoints: inclusion criteria were defibrillator implants prior to 1st January 1997. Exclusion criteria were cardiac resynchronisation therapy indications at defibrillator implantation. Failure of active follow up prior to 60 months from implant. Primary end point was development of cardiac resynchronisation therapy criteria heart failure within 60 months of first implant.

Investigation: ejection fraction was calculated by contrast ventriculography or on the apical four chamber view on transthoracic echocardiography.

Contrast ventriculography, undertaken with a Siemens Hicor laboratory. Ejection fractions calculated from RAO projection by assisted endocardial definition in systole and diastole.

Echocardiography, using the Sonos 2500 (Hewlett Packard) measurements were taken in parasternal short and long axis and apical four, two and three chamber views. From nine-segment analysis of wall motion LVEF was estimated. This method is validated against radionucleide techniques(131).

ECG, QRS duration was assessed in leads II, V1 and V6: the median of these was recorded.

Follow up, biannual outpatient follow up with additional visits as clinically indicated was performed with regular 12 lead surface ECG. Planned outpatient attendances and clinical events were recorded.

Data collection, prescribed medication, NYHA class, LV function and QRS duration was recorded. This information was entered for implantation, generator change and most recent hospital attendance. Date cardiac resynchronisation therapy criteria were met was recorded.

Statistical analysis, proportion progression was compared in different groups and confidence intervals for these proportions calculated using the Wilson method. Between group comparisons were made using Chi square analysis.

4.3.5 Results

Eighty-nine patients were implanted prior to 1st January 1997.
Excluded were cardiac resynchronisation therapy criteria at implant (n=3), death within 60 months of implant (n=14) and follow up at outside our service (n=12).

Features at implant of individuals progressing to cardiac resynchronisation therapy criteria within 60 months are compared with those who did not fulfil the criteria Figure 4.9.

Nine patients (14%) developed cardiac resynchronisation therapy criteria. Five (8%) developed cardiac resynchronisation therapy criteria within 60 months (CI 4-18%). The nine patients who developed cardiac resynchronisation therapy criteria were prescribed

beta blockers and ACE inhibitors unless contra indicated. One failed to tolerate ACE inhibitors, four were unable to be maintained on beta blockers.

Progression was commoner among those with impaired LV function (LVEF<35%) and those with impaired conduction (QRS>130 msec), Figure 4.10↵. Individuals with LVEF below 35% and QRS durations greater than 130 msec have a 36 (CI 16-61)% chance of developing cardiac resynchronisation therapy criteria within 60 months of implant.

4.3.6 Discussion

There is accumulating evidence of cardiac resynchronisation therapy inducing reverse remodelling of myocardium, increasing ejection fraction and reducing LV dimensions(126;127). This combined with the suggestion that cardiac resynchronisation therapy may reduce heart failure mortality(132;132) (although no single reported trial has demonstrated this) creates an imperative for eligible patients to be implanted with a minimum of delay and the use of cardiac resynchronisation therapy at the earliest possible stage to be investigated in clinical trials.

Patients undergoing defibrillator implantation are an ideal group to explore the management of the early heart failure group and this report establishes a baseline.
It has previously been suggested that the rate of progression to cardiac resynchronisation therapy among defibrillator recipients is 16%(133). This was based on three year follow up and cardiac resynchronisation therapy indications of NYHA II or worse heart failure with confirmed LVEF<35% and QRS>120 msec.

Our data for 5 year follow up reveals a lower overall progression 8 (CI 4-18)% using the more rigorous standard of NYHA III-IV and QRS>130 msec.

All the patients who developed cardiac resynchronisation therapy criteria within five years had severely impaired left ventricular function and QRS>130 msec at the time of implantation.

We have shown that selecting those with poor LV function and a prolonged QRS complex significantly predicts progression to cardiac resynchronisation therapy criteria compared with those with normal conduction and LV function: the proportion progression in this group is 36%.

The identification of those individuals likely to progress to develop cardiac resynchronisation therapy criteria within five years is a useful exercise. Knowing which individuals are at high risk of developing cardiac resynchronisation therapy criteria gives the implanter four options: inserting a single chamber defibrillator, inserting a dual chamber defibrillator, inserting a cardiac resynchronisation therapy capable device (capping the LV port) and inserting a cardiac resynchronisation therapy-defibrillator and LV lead.

The first two options are the cheapest and quickest at the outset but leave the patient a high risk of requiring upgrade to cardiac resynchronisation therapy-defibrillator within the lifetime of the device.

The third option may provide a cost benefit, when upgrade is required the device may be preserved and an LV lead deployed. This provides no direct benefit to the patient as re operation is still required.

In options one, two and three attempted upgrades may fail due to the technical problems in instrumenting through a subclavian vein that already contains chronic leads. Additionally a complex revision would be required on a patient with NYHA III-IV symptoms as opposed to a potentially simpler implant on a NYHA I-II patient.

The fourth option is the most expensive and time consuming at the outset but provides the greatest potential benefit to the patient. LV lead placement at defibrillator implantation avoids the requirement for an additional invasive procedure on a patient with moderate to severe heart failure (a procedure they may be too unwell to undergo). It is also less technically demanding than an additional lead placement. A potential barrier to implanting

the LV lead at outset in a cohort the majority of who will not develop indications for cardiac resynchronisation therapy is the perceived high risk nature of the procedure with concerns over coronary sinus dissection leading to tamponade and even death. In fact the procedure is in fact extremely safe with very low rates of major complications(119).

Options three and four applied to all defibrillator recipients are extremely unlikely to provide cost or overall clinical benefit as only 8% will require upgrading. These strategies are suitable only for groups with a higher risk of developing cardiac resynchronisation therapy criteria. *Study limitations:* these individuals had devices inserted prior to 1997, at the end of which period UK implant rates had still not reached 8 per million. The report is inevitably therefore generated from a small cohort. Since 1997 the indications for defibrillator implantation, and consequently the population concerned, have changed. The recent expansion in recognised defibrillator indications has focussed on those with impaired LV function(21) so the proportion of defibrillator patients in whom cardiac resynchronisation therapy indications are either met at the outset or develop during the lifetime of their devices is likely to be higher now than it was five years ago.

4.3.7 Conclusion

The overall progression to cardiac resynchronisation therapy criteria among the patients with defibrillator after 5 years is 8% (CI 4-18%).

QRS>130 msec and LVEF<35% are significant predictors of the development of cardiac resynchronisation therapy criteria.

In patients with QRS durations over 130 msec and LVEF<35% the rate of progression to cardiac resynchronisation therapy criteria within 5 years is 36% (CI 16-55 %).

Figure 4-9 Comparison of Progressors and Non progressors Baseline Characteristics.

	Progressors	Non progressors
Number	5	55
Male %	70	60
Age (SD) years	53 (15)	60 (8)
Aetiology (%)		
IHD	80	57
DCM	20	2
Other*	0	41
QRS Duration (%)		
>130 msec	100	73
<130 msec	0	27
LVEF (%)		
<35%	100	45
>36%	0	55
NYHA (%)		
Class 0 or I	20	73
Class II	80	20
Class III or IV	0	7

*Other aetiologies comprised: structurally normal hearts (n=12), right ventricular dysplasia (3), hypertrophic cardiomyopathy (5), congenital heart disease (2), valvular heart disease (1).

IHD: ischaemic heat disease, DCM: dilated cardiomyopathy, NYHA: New York Heart Association.

Figure 4-10 Proportion Progression by Baseline Conduction and EF Abnormalities

Subgroup	Number	Progression %	Significance
Entire Cohort	60	8	
LV function			
EF>36%	32	0	
EF <35%	28	18	p=0.018
Conduction msec			
<129	41	0	
>130	19	26	p=0.002
Combined Measure			
QRS>130 and EF<35%	14	36	
Other	46	0	p<0.001

5 PILOT STUDIES PERFORMED DURING THE COURSE OF THE THESIS

The configurations piloted are summarised in Figure 5.1↵.

5.1 Left Pulmonary Artery Cathode Defibrillation in Pigs

Aims: to examine the impact of a incorporating a coil electrode placed in right pulmonary artery into defibrillation cathode. *Methods:* two anaesthetised pigs had standard RV/SVC electrodes and an active housing implanted. Defibrillation coils were also advanced to left pulmonary artery and middle cardiac vein. Defibrillation threshold was assessed for: RV to SVC and active housing, for RV to left pulmonary artery and SVC and for Middle cardiac vein to SVC and left pulmonary artery. *Results:* there was no decrease in defibrillation threshold using the pulmonary artery configurations in the two animals. *Reason for Abandonment:* Left pulmonary artery is not an attractive site for clinical lead placement. Although it is not proven that this site does not reduce defibrillation threshold any decrease must be modest and inconsistent, not of the level necessary to overcome the drawbacks of the site. *Interpretation:* it is likely that a degree of current shunting is occurring through the great vessels. This leads to current bypassing myocardium preventing the theoretically improved vector from reducing defibrillation threshold.

5.2 Multiple Passive Electrodes in Middle Cardiac Vein Defibrillation

Aims: to examine the benefit of multiple middle cardiac vein bystander electrodes on microfilament anodal middle cardiac vein defibrillation. *Methods:* three pigs were anaesthetised and a right ventricular endocardial electrode, active housing and microfilament middle cardiac vein electrode implanted. Defibrillation threshold was assessed for the configuration middle cardiac vein to active housing with and without the addition of six balance middle weight angioplasty guide wires spread through the tributaries of middle cardiac vein. *Results:* Defibrillation thresholds were: monofilament 11.0 ± 2.2 Joules and monofilament + passive 8.9 ± 0.22 Joules (p 0.08). This represented a 19% (95% CI –0.4-37%) decrease in defibrillation threshold. *Reasons for Abandonment:* Although a strong trend toward a decrease in defibrillation threshold was demonstrated this was no greater than the trend with one passive electrode despite significantly greater complexity. *Interpretation:* Guide wires have a smaller surface area than custom designed microfilament electrodes and the potential added benefit of multiple bystanders might have been reduced by resorting to an inferior electrode. The protocol was not possible using microfilaments as they were not sufficiently manoeverable.

5.3 Left Ventricular Endocardial Anodal Defibrillation in Pigs

Aims: to examine left ventricular endocardial defibrillation. *Methods:* four pigs were anaesthetised and implanted with RV/SVC defibrillation electrodes, an active housing and a middle cardiac vein electrode. The right carotid artery was accessed by cut down and 9F MPA catheter introduced. A defibrillation coil (identical to the middle cardiac vein electrode) was introduced through this into the left ventricular apex. Defibrillation threshold was assessed for three anodes; middle cardiac vein, RV and left ventricle, all to an SVC and active housing cathode. *Results:* three animals died before the protocol could be completed, in the remaining animal defibrillation threshold higher than that of middle cardiac vein but lower than that of RV. *Reason for Abandonment:* The attrition rate of three out of four made the protocol neither practical nor ethical. Interpretation: It is likely that occlusion of the carotid artery was causing animals to die of cerebral infarction. The mode of death in all three animals was a sudden decrease in blood pressure with in minutes of cannulation of the carotid artery. Further exploration of the concept of left ventricular endocardial defibrillation would be possible with a long lead defibrillation electrode.

5.4 Anterior Cardiac Vein Defibrillation

Aims: to establish the value of incorporating an anterior cardiac vein electrode into a defibrillation circuit. *Methods:* two pigs were anaesthetised and had RV/SVC defibrillation electrodes and an active housing inserted. Defibrillation electrodes were placed in middle cardiac vein and anterior cardiac vein. Defibrillation thresholds were assessed for; RV to SVC and active housing, middle cardiac vein to anterior cardiac vein, middle cardiac vein and anterior cardiac vein to SVC and active housing. *Results:* no configuration tested yielded defibrillation thresholds below that of RV to SVC and active housing in both animals. One animal could not be defibrillated in any of the configurations involving anterior cardiac vein as cathode. *Reason for abandonment:* The small potential benefit of middle cardiac vein to anterior cardiac vein did not appear to justify further study. The anterior cardiac vein cathode configurations showed no promise. *Interpretation:* anterior cardiac vein to active housing appears to bypass myocardium compromising defibrillation. Although middle cardiac vein to anterior cardiac vein appears to have the advantage of shocking straight through the interventricular septum it is likely lateral walls of both ventricles experienced low current density and may have been foci for re-initiation of fibrillation.

5.5 Sole Anodal Lateral Cardiac Vein Defibrillation in Man

Aim: to asses the efficacy of sole anodal lateral cardiac vein defibrillation in man. Methods: One patient was implanted with a defibrillator, a RV/SVC electrode and a defibrillation electrode advanced into lateral cardiac vein. Defibrillation threshold was assessed for the configurations RV to SVC and active housing and middle cardiac vein to SVC and active housing. *Results:* the defibrillation threshold was 25 Joules for lateral cardiac vein and 9 Joules for RV. External shocks were required twice during the defibrillation threshold determination for lateral cardiac vein due to failed maximum output rescue therapies. *Reason for abandonment:* It was not ethical to submit further patients to potentially multiple external rescue and prolonged fibrillation. *Interpretation:* The lateral cardiac vein is too anterior for reliable defibrillation, current bypasses the myocardium and defibrillation loses efficacy.

Figure 5-1 Configurations Piloted

Anode	Cathode	Model	Subjects	DFT (J)
MCV+Passive	SVC+AH	Pig	3	8.9
RV	LPA+SVC	Pig	2	17.5
MCV	LPA+SVC	Pig	2	17
LV	SVC+AH	Pig	1	12
MCV	ACV	Pig	2	13.5
MCV	ACV+SVC	Pig	1	17
MCV+ACV	SVC+AH	Pig	2	23.5
MCV	ACV+AH	Pig	2	29
MCV+ACV	SVC	Pig	1	>34
LCV	SVC+AH	Man	1	25

Abbreviations used in table 6.1: RV right ventricle, LV left ventricle, MCV middle cardiac vein, LPA left pulmonary artery, ACV anterior cardiac vein, SVC superior cardiac vein, AH active housing, DFT defibrillation threshold J joules.

6 DISCUSSION

6.1 Discussion of Results

Research interest in defibrillation threshold has been declining since 1999, figure 6.1↵. There are several reasons for this; high defibrillation thresholds are no longer the clinical problem they were, device longevity is approximately five years (and as such quite acceptable) charge times to maximum output therapies may be as low as six seconds and device sizes are now only 30 cubic centimetres for a typical dual chamber model. Furthermore it is becoming apparent that the holy grail of painless defibrillation, which would require outputs of under one Joule, may not be a realistic goal. There are also many strategies available to combat high defibrillation thresholds in clinical practise; options available include superior vena cava coils, high output devices and subcutaneous arrays. Implant techniques which are expensive, time consuming or technically challenging must offer more than a modest defibrillation threshold reduction to enter routine practice. Given that coronary venous defibrillation is likely to yield only a modest reduction in defibrillation threshold, if any at all, any future it has lies in reducing the additional complexity of the procedure required to facilitate it and/or combining defibrillation with other functionalities.

Transvenous delivery of cardiac resynchronisation therapy requires the implantation of a pacing lead into a coronary vein. Adding a defibrillation functionality to this lead would potentially allow auxiliary coronary venous defibrillation without any increase in the number of electrodes required. There will inevitably remain issues of technical difficulty both in engineering and placing the lead but these are unlikely to prove insurmountable. Such an approach has been studied previously and a dramatic reduction in defibrillation threshold was observed. In order to achieve these benefits with the lead technology available the investigators found it necessary to administer two separate capacitance therapies, first a 20% discharge through the coronary venous lead followed by the

remaining 80% from the RV electrode(101). Building such complexity into the system negates many of the potential benefits of coronary venous defibrillation.

In studying defibrillation threshold it is conventional to quote the mean or median value. In fact when device outputs are set the manufacturer must consider the 95^{th} centile defibrillation threshold. Thus a configuration which decreases average defibrillation threshold but increases the standard deviation or interquartile range so that the 95^{th} centile remains unchanged is of limited clinical value. Conversely a configuration which does not alter average defibrillation threshold but reduces variability and therefore 95^{th} centile values would allow systems with lower maximum outputs to be designed.

The passive electrode affect was regarded as an entirely negative phenomenon prior to this thesis. Studies had demonstrated that bystander epicardial patch electrodes had the ability to increase defibrillation threshold of therapies delivered from a transvenous coil electrode. No equivalent effect was demonstrated when a bystander endocardial coil was substituted for the epicardial patch and as such electrodes were of historical interest only research attention to the passive electrode affect ceased. The possibility that bystander electrodes may have a beneficial impact on defibrillation threshold through a passive electrode affect does not appear to have been previously considered. The potential of harnessing such a phenomena is in the ability to deploy filaments, without the need for proximal connections, which may reduce the defibrillation threshold of a configuration. It unlikely that such a strategy would be useful in endocardial defibrillation but the branching structure of the coronary sinus offers the possibility to utilise the passive electrode affect as demonstrated in this thesis.

I propose two conditions that must be fulfilled for a passive electrode affect to alter defibrillation threshold:

(i) The impedance of the composite passive electrode (bystander electrode and tissue between bystander an active electrode) must be low enough relative to

the active electrode that an appreciable proportion of current is drawn through the bystander electrode.

(ii) The alteration in field characteristics created by the passive electrode must be of a nature which alters defibrillation efficacy.

A bystander electrode fulfilling condition (i) but not (ii) may alter impedance but will not impact on defibrillation threshold.

The alteration of defibrillation efficacy may be impact positively or negatively on defibrillation threshold. In the bystander epicardial patch electrode studies current was drawn from the cathode in the opposite direction to the cathode; defibrillation threshold increased(99;104). In the previously published endocardial bystander electrode study there was a modest trend to a reduction in impedance but no affect on defibrillation threshold(87). It is likely condition (i) was fulfilled but the active and bystander electrodes were so close condition (ii) was not.

The studies in this thesis examining defibrillation threshold have been consistent with this interpretation of the published data. Study 3.1 examined the ability of an electrode in an adjacent branch of middle cardiac vein to an active electrode to alter defibrillation threshold. A 24% reduction in defibrillation threshold was seen with a corresponding fall in impedance. This proves a passive electrode affect may decrease defibrillation threshold, the main limitations of the study relate to how far this differs from a clinical system. To facilitate transvenous lead placement in two adjacent radicles a custom designed micro filament electrode was utilised, this electrode had unusual electrical properties which made it unsuitable for use as a sole anode. In a subset of animals the delivery of energy above a certain threshold caused an increase in impedance preventing full energy delivery. In animals in which this threshold came below the defibrillation threshold defibrillation was not effected. I believe it may have been precisely this property that allowed the passive

electrode affect to occur in this configuration; during current delivery impedance in the active electrode rose favouring current transfer to the bystander electrode.

Chapter 3.3 formed the second examination of the phenomena in this thesis. Defibrillation threshold was determined for the RV →SVC and active housing configuration with and without a bystander middle cardiac vein electrode in place. The electrode used was of the same properties as that used for the human studies. No passive electrode affect was seen on either defibrillation threshold or impedance, leading to the conclusion that condition (i) was not satisfied.

In comparing this configuration to previous studies demonstrating a passive electrode affect it differs from the epicardial patch protocols in the nature of the electrode. The impedance of the bystander coil and intervening tissue was too great to draw a significant proportion of current away from the normal vector. This is a reflection of properties of the electrodes rather than positioning as epicardial patch electrodes over middle cardiac vein do exert a passive electrode affect. In comparing studies 3.1 and 3.3 there are two salient differences; the nature of the active electrode and the position of the active electrode. It is not known whether delivering defibrillation attempts from RV endocardium with a microfilament electrode would have allowed a middle cardiac vein bystander coil to exert a passive electrode affect, nor is it known whether the electrode used in 3.3 if placed in adjacent branches of middle cardiac vein would exert a passive electrode affect. Neither of these hypothesis was possible to test under the conditions of the license and model for technical reasons, the microfilament is unsuited to endocardial placement as it would not be stable for multiple defibrillation attempts and it was not possible to place two of the larger calibre leads into middle cardiac vein despite several attempts.

The role of virtual electrodes in the passive electrode affect remains undefined. Internal defibrillation thresholds would be orders of magnitude greater than they are were it not for the formation of virtual electrodes in myocardium. In a homogenous substrate energy

density decays exponentially with distance from a point source such that were it not for the formation of virtual electrodes maintaining a low impedance in myocardium during administration of energy only areas in close proximity to the electrodes would be subjected to significant current density. For a bystander electrode to exert a passive electrode affect a composite electrode must be formed consisting of the active electrode, the bystander electrode and a virtual electrode of the intervening tissue. Any in vitro or computer model of the passive electrode affect must take this into account to be regarded as valid, modelling involving a homogenous electrolyte solution is not equivalent to the specified conditions.

A limitation of human studies of defibrillation threshold has been the precision and repeatability of the values obtained. What the defibrillation threshold obtained corresponds to may be anything between ED_{75} and ED_{99} so long as it has a resolution and repeatability of around four Joules. The evidence from the animal study in this thesis suggests that a limited induction defibrillation threshold determination has significant benefits in reducing energy and fibrillation time requirements over a binary search. The similarity in defibrillation threshold value obtained between the limited induction protocol and the full binary search is, at first sight, surprising. It is explicable by two factors; firstly the limited induction protocol is a form of binary search with steps up within inductions and steps down between inductions. Secondly the step up aspect which biases the protocol toward a lower defibrillation threshold is balanced by the long fibrillation times before later defibrillation attempts which will tend to increase risk of therapy failure. Many variations of the limited induction protocol are possible, adding a fourth induction, performing a true binary search after a limited induction and variations of therapy sequences will all require separate validation in appropriate models. The value of this protocol is as a replacement for limited binary searches in clinical studies, if validated in humans the number of patients

required for clinical studies in which defibrillation threshold is primary end point would be reduced.

The human acute defibrillation studies in this thesis were disappointing. The middle cardiac vein did not offer any defibrillation efficacy benefit over RV apex contrasting with the porcine results. This discrepancy is explained by middle cardiac vein's higher impedance and oblique orientation in man. The auxiliary lateral vein protocol also yielded disappointing results and interpretation of this is hindered by inability to calculate the proportion of current directed via the auxiliary route. From first principals resistors in parallel have a reciprocal total impedance equal to the sum of the reciprocals of the individual resistors. From the pig study 3.2 and the human data it may be seen that this rule does not apply, probably due to some unknown interaction of the auxiliary and main shock in the myocardium. Dedicated circuitry controlling the current split is required to determine the optimal apportionment.

We have demonstrated in the implantable cardioverter defibrillator population that selecting out a subset with prolonged QRS durations and impaired ventricular function allows a group at high risk of developing cardiac resynchronisation criteria to be identified. Criteria for resynchronisation therapy are likely to become a moving target over the next decade as QRS duration is replaced by a more specific and sensitive measure of response to biventricular pacing. Of less certainty but more interest is whether the symptom severity stipulation is removed so that prophylactic resynchronisation therapy becomes practised. There is a definite rationale behind such a move, cardiac resynchronisation is shown to reverse remodel ventricles, can it prevent remodelling and thereby deterioration? The ideal group of patients in which to test this hypothesis are those being implanted with a device, either defibrillator or pacemaker, as they require only an amendment to an existing procedure.

6.2 Limitations Of The Study

The limitations of each of the experimental chapters are discussed in the relevant chapters. These fall under three main categories:

(i) Experimental model

(ii) Accuracy of defibrillation threshold testing

(iii) Sample sizes

There is a striking discrepancy in the results of middle cardiac vein defibrillation between humans and swine. Initially this was attributed to the higher impedance of the custom designed leads used for human studies. In this thesis the electrode used in animal chapters 3.2 and 3.3 is the same as that used in the human experiments in chapters 4.1 and 4.2. The discrepancy must therefore be attributed to the limitations of the model. The variation between humans and pigs most likely to explain the discrepancy is the difference in impedance and orientation of the heart within the thorax. The higher impedance of MCV defibrillation in man reduces current flux for a given energy. In humans the interventricular septum (and middle cardiac vein) point toward the mid clavicular line (or more lateral in dilated hearts). In pigs the interventricular septum and middle cardiac vein point toward the sternum. The vector in pigs from middle cardiac vein to active housing drags current through the left ventricle and septum. The vector to superior vena cava takes current straight through the septum. In humans the change in orientation creates a vector of middle cardiac vein to active housing passing through the septum and right ventricle and the middle cardiac vein to superior vena cava vector also biases the right ventricle. It may be the benefit in the pig was derived from better defibrillation of not only septum but also left ventricle and it is this component that is lost in the human middle cardiac vein vector. If this assumption is correct the problem should be surmountable by moving the cathode to recreate the porcine vector. This would probably require a subcutaneous array or active housing in the auxiliary region and the superior vena cava electrode either omitted or

replaced by a pulmonary artery coil. Such systems are unlikely to be acceptable to operators or patients. The middle cardiac vein also proved far more complex to access in humans than pigs, in two studies, chapter 4.1 and the previously referenced study(103), out of 18 patients recruited five could not be implanted with middle cardiac vein electrodes. Whilst this would be likely to be overcome with experience (middle cardiac vein is a constant anatomical feature) the combination of this complexity, two negative studies and the increasing realisation of it's inferiority as a resynchronisation site are a strong disincentive to further defibrillation research from this site.

Accuracy of defibrillation threshold testing is a significant limitation of the studies of human coronary venous defibrillation. In the chapter 3.4 we were able to ascertain that a limited binary search likely to be slightly more repeatable than the one used for our human studies had an intra subject variability of 25%. This reduces the power of the study to detect significant differences. It should be considered however that clinically significant and consistent differences were being sought, not statistically significant but minor or inconsistent reductions.

Sample size was a factor in study 3.4 and all the human protocols. In the human defibrillation studies, as discussed above, it is apparent that a clinically significant benefit was not going to be present and confidence intervals are quoted to illustrate this. Confidence intervals are also quoted in 3.3 to define the impact of the small sample size in this study. In protocol 3.4 sample size was limited by resources, enough data was acquired to justify taking the algorithm developed into human trials which is where the benefit lies.

6.3 Conclusions

A bystander electrode adjacent to a mono-filament electrode in MCV reduces DFT by 24% compared to monofilament MCV alone.

Micro-filament electrodes decrease DFT as auxiliary anode but not as sole anode.

With appropriate lead design defibrillation middle cardiac vein anodal configurations that do not involve crossing any heart valve may produce low DFT compared to conventional configurations.

In a porcine model there is no evidence that a defibrillation coil placed in the mid cardiac vein will affect the defibrillation threshold of a shock therapy delivered from the RV.

A limited induction multiple test therapy algorithm derives a defibrillation threshold of greater reproducibility than the limited (clinical) binary search with substantially reduced ventricular fibrillation time, inductions, therapies and total energy administration compared to the full multiple reversal binary search.

In humans the middle cardiac vein is an effective site for defibrillation coil placement in acute circumstances. This justifies further research toward entirely transvenous systems: pacing, resynchronisation and defibrillation may be possible without crossing any heart valves.

Lateral cardiac vein auxiliary defibrillation may increase defibrillation threshold in the absence of circuitry to control the current distribution between the two anodes.

The overall rate of progression to cardiac resynchronisation therapy criteria is 8% at 60 months. Those patients with LVEF <35% and QRS duration >130 msec have a 36% chance of developing resynchronisation criteria within five years of defibrillator implant. Consideration should be given to implanting resynchronisation capable devices in these patients at the time of initial defibrillator implantation.

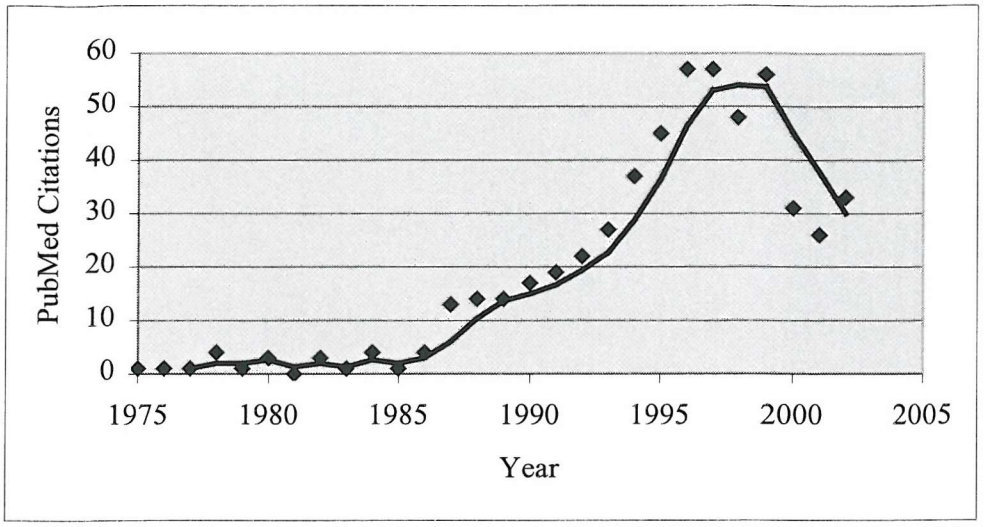
6.4 Future Research Directions

Coronary venous defibrillation in humans may undergo further investigation in two areas, as a combination with resynchronisation therapy and in a limited niche of patients with right ventricles not suitable for endocardial electrode placement. The combination with resynchronisation will require the development of leads with effective defibrillation coils and pacing electrodes capable of being placed in cardiac veins. It assumes that a defibrillation threshold reduction and leads stability can be demonstrated in long term studies. In those with morphologically abnormal right ventricles who currently require epicardial defibrillation electrode placement the middle cardiac vein may represent a transvenous alternative, the number of individuals in whom this is indicated will probably be too small for industry to fund product development of such a clinical lead. This assessment is based on an interpretation of the findings of this thesis that middle cardiac vein defibrillation does not show obvious advantages in humans. There is a possibility that this is an incorrect conclusion and that there are subtleties of variables such as lead placement which will allow the promising porcine results to be replicated in humans, should this be the case the issues of technical failure rate would need to be overcome. Defibrillation threshold determination algorithms currently in operation have number of disadvantages for human use, those which give an accurate repeatable and precise results require prohibitive time in ventricular fibrillation and number of therapies. Using upper limit of vulnerability testing as an alternative does not reduce they number of fibrillation episodes and may even require more total energy delivery to determine an accurate threshold. The utility of the limited induction protocol is self evident. I propose a validation study in humans in which the limited induction protocol be performed twice in each subject to demonstrate its repeatability.

The exploration of resynchronisation at an earlier stage requires large scale clinical trials to assess potential clinical benefit and cost efficacy. I have proposed randomisation

of defibrillator recipients with NYHA I-II symptoms, conduction delay and left ventricular impairment to either standard or resynchronisation devices. Endpoints would be hospitalisations and functional capacity after three years. Such a study would require over 800 inclusions necessitating international cooperation and commercial sponsorship.

Figure 6-1, Defibrillation Threshold Citations by Year



6.5 Publications Arising

6.5.1 Abstracts

Paisey JR, Moore R, Allen S, Roberts PR, Morgan JM.

Indications for resynchronisation therapy in patients with implantable cardioverter defibrillators. Heart 87 Supp II p60

Paisey JR, Roberts PR, Allen S, Morgan JM.

Assessment of defibrillation via the middle cardiac vein in pigs. Eur Heart J 23 Abstr Suppl P3480 and Europace 3 suppl A6

Paisey JR, Moore R, Roberts PR, Morgan JM.

Predictors and rate of progression to resynchronisation criteria in ICD recipients. Circulation 106 19 II-1-II-646.

Paisey JR, Roberts PR, Yue A, Betts TR, Allen S, Cheatle L, Bonner MD, Whitman T, Morgan JM.

Evaluation of The Efficacy Of Coronary Venous Defibrillation In Man. PACE. 2003 Feb;26(2)Part II S179 and PACE 2003 26;4(II)

Paisey JR, Yue A, Allen S, Bessoule F, Betts T, Roberts PR, Morgan JM. Efficacy of Transvenous Coronary Venous Defibrillation in Man. Heart 2003 89 Supp I A20

Paisey JR, Elkins K , Yue A, Betts T, Roberts PR, Morgan JM.

The Prevalence of Criteria for Prophylactic ICD Implantation. PACE 2003 26;4(II) 448 and Europace Volume 4, Supplement 2, December 2003, Page B183

Paisey JR, Yue A, Bessoule F, Roberts PR Morgan JM.

Defibrillation Threshold Reduced By Middle Cardiac Vein Defibrillation Using Novel Electrode. Europace , Volume 4, Supplement 2, December 2003, Page B89

Paisey JR, Yue A, Betts T, Roberts PR Morgan JM.

A Novel Algorithm For Defibrillation Threshold Assessment Using Minimal VF Inductions. Europace, Volume 4, Supplement 2, December 2003, Page B182

Paisey JR, Yue A, Bessoule F, Roberts PR Morgan JM.

Human Sole Anode Middle Cardiac Vein Defibrillation. Europace Volume 4, Supplement 2, December 2003, Pages B88-B89

6.5.2 Peer Reviewed Articles

Paisey JR, Yue AM, Moore R, Betts TR, Roberts PR, Morgan JM.

Development of indications for cardiac resynchronisation therapy in the implantable cardioverter defibrillator population Int J Cardiol 2005 Mar 18;99(2):187-90

Paisey JR, Yue AM, Bessoule F, Allen S, Roberts PR, Morgan JM.

Examination of a novel middle cardiac vein defibrillation coil as stand alone anode, auxilliary anode and bystander electrode in a transvenous defibrillation circuit. Pacing Clin Electrophysiol. 2004 Aug;27(8):1089-93.

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