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Effect of Drugs on Defibrillation Capacity

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Abstract

Over 300 000 people die of sudden cardiac death (SCD) in the US annually. Implantable cardioverter-defibrillators (ICDs) have been shown to be more effective than antiarrhythmic drugs for the prevention of SCD in specific susceptible populations. Many patients in whom ICDs have been implanted receive concomitant therapy with antiarrhythmic drugs, for the purpose of reducing the frequency of appropriate and inappropriate defibrillation shocks. Drugs may influence defibrillation capacity and therefore influence the function of ICDs. The objective

of this article is to review and update the literature regarding the effects of drugs on defibrillation capacity.

A literature search was performed using PubMed (1966 to December 2007) to identify clinical studies, case reports and animal studies describing the effects of drugs on defibrillation capacity. Search terms included: antiarrhythmic drugs; cardiovascular drugs; amiodarone; sotalol; flecainide; propafenone; dofetilide; ibutilide; β-blockers; lidocaine; procainamide; N-acetylprocainamide; mexiletine; disopyramide; moricizine; calcium channel blockers; defibrillation threshold; defibrillation energy requirements; defibrillation energy changes; defibrillation efficacy; implantable cardioverter defibrillators; and external defibrillators.

Evidence from clinical studies indicates that amiodarone may increase defibrillation threshold (DFT). In addition, some data indicate that drugs including lidocaine, mexiletine, moracizine (moricizine), verapamil, venlafaxine and anaesthetic agents may increase DFT. In contrast, agents including sotalol, dofetilide and β-adrenergic receptor antagonists (β-blockers) may reduce DFT. Propafenone and procainamide appear to have minimal effect on DFT. For those antiarrhythmic drugs with both sodium and potassium channel blockade (e.g. amiodarone), the effect of sodium channel blockade predominates, resulting in an increase in DFT.

Numerous drugs may affect defibrillation capacity. These effects must be considered when managing patients who have an ICD and require concomitant pharmacotherapy.

1. Introduction

Use of implantable cardiac devices is increasingly common and widespread. The American Heart Association (AHA) reported that nearly 68 000 patients in the US underwent an implantable cardioverter-defibrillator (ICD) procedure in 2004.[1] As many as 50% of patients in whom ICDs have been implanted receive concomitant antiarrhythmic drug therapy.[2] The potential exists for adverse interactions between ICDs and drugs, in some cases resulting in unanticipated device behaviour, which may lead to significant adverse clinical outcomes. The purpose of this article is to provide an updated, evidence-based review of the effect of drugs on defibrillation capacity.

1.1 Clinical Guidelines and Indications for Implantable Cardioverter-Defibrillators

In 2002, the American College of Cardiology (ACC), AHA and the North American Society for Pacing and Electrophysiology (NASPE) [now known as the Heart Rhythm Society (HRS)] published the Guideline Update for Implantation of Pacemakers and Antiarrhythmia Devices,[3] in which specific recommendations for ICD implantation were provided. In 2005, the ACC and AHA,[4] the European Society of Cardiology (ESC)[5] and the Heart Failure Society of America[6] published guidelines for the long-term treatment of heart failure. Each set of guidelines provides recommendations regarding the implantation of ICDs, although there are discrepancies between them. For example, ICD implantation in patients who develop left ventricular dysfunction (LVD) with a left ventricular ejection fraction (LVEF) of ≤30% and a New York Heart Association (NYHA) class of either II or III following a myocardial infarction is associated with a class IB recommendation/level of evidence based on the 2005 ACC/AHA heart failure guidelines,[4] a class IA recommendation/level of evidence from the 2005 ESC heart failure guidelines[5] and a class IIb from the 2002 ACC/AHA/NASPE pacemaker and defibrillator guidelines. In an attempt to resolve

these inconsistencies, the ACC, AHA and ESC released Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death in 2006.[7] These new guidelines classify the patient population described here as class I with an evidence level of A. A detailed review of the guidelines for ICD implantation is beyond the scope of this article; the guidelines are readily available for review.[3-7]

ICD technology and indications have changed substantially over the past 10 years as more data regarding safety, efficacy and mortality effects have become available. Current ICDs have longer battery lives, faster capacitor charge times, software for memory and specialized arrhythmia detection algorithms. These devices are capable of storing supraventricular and ventricular tachyarrhythmia episodes for physicians and device check specialists to review during subsequent interrogations. These data are useful to determine if therapies were delivered and if delivered therapies were appropriate. Along with these data, patient histories may assist in the identification of potential triggers that may have initiated the episode(s). In addition, ICDs store histograms that can provide details about patients' heart rates and rhythms. Detection algorithms have decreased the number of inappropriate shocks delivered for supraventricular tachyarrhythmias and have allowed for more sophisticated programming options.

Several primary prevention studies have been conducted in which the efficacy of ICDs for decreasing mortality in patients at risk of sudden cardiac death (SCD) has been evaluated.[8-13] ICDs have been shown to be more effective than antiarrhythmic agents for mortality reduction; indeed, antiarrhythmic drugs may increase the incidence of mortality.[13-16] The results of the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) showed that, in patients with NYHA class II or III heart failure and a LVEF ≤35%, amiodarone had no favourable effect on survival, whereas a single-chamber ICD (single lead in the right ventricle) reduced overall mortality by 23%.[13] The results of this study suggest that nearly 500 000 Medicare beneficiaries are eligible for an ICD.[17] Results of this and other primary prevention trials have driven the changes in the 2006 ACC/AHA/ESC guideline updates for the management of patients with ventricular arrhythmias and the prevention of SCD.[7]

In 2001, the US FDA approved another device therapy that has produced positive mortality and morbidity effects in patients with heart failure. Cardiac resynchronization therapy (CRT), also known as biventricular pacing, attempts to resynchronize the right and left ventricle in situations in which an interventricular or intraventricular conduction disturbance has caused mechanical dyssynchrony. Current indications for CRT include moderate to severe heart failure (NYHA class III or IV) with a wide QRS complex (>120 ms) while receiving optimal medical therapy.[18] The CARE-HF (Cardiac Resynchronisation in Heart Failure) trial found that CRT reduced combined all-cause mortality or an unplanned hospitalization by 37% and reduced all-cause mortality by 36%.[19] In addition, CRT reduced the risk of hospitalizations due to heart failure exacerbations and improved symptoms and quality of life.[20] While the primary goal with biventricular therapy is to pace the right and left ventricles 100% of the time, some devices are manufactured with larger capacitors in order to defibrillate the heart. The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial[21] compared standard medical therapy for heart failure with either a biventricular pacemaker or biventricular defibrillator. Results showed a statistically significant difference with both the biventricular pacemaker and defibrillator compared with standard medical therapy for the primary composite endpoint of a reduction in death from or hospitalization for any cause.[21] The majority of the devices implanted today for use in patients with heart failure are biventricular ICDs or CRT defibrillators, because up to 50% of these patients are at risk for SCD.[7]

1.2 Drugs as Adjuvant Therapy in Patients with Implantable Cardioverter-Defibrillators

Despite the clear benefits of ICDs, the need for acute and long-term management with medications

has not been eliminated. While prospective studies have not investigated the potential mortality benefits of concurrent therapy with medications and implantable cardiac devices, evidence indicates benefit associated with antiarrhythmic drugs in patients with ICDs. In a retrospective review of medical records of 360 patients undergoing concomitant therapy with antiarrhythmic drugs and an implanted ICD, Ho et al.[22] demonstrated that use of a β-adrenergic receptor antagonist (β-blocker) was associated with increased survival rates. Amiodarone and sotalol were associated with neutral effects on survival. Many clinicians approach patient management using a hybrid therapy, with the goals of therapy to reduce the incidence of supraventricular or ventricular arrhythmias and ICD shocks and, as a secondary benefit, prolonging ICD battery life.[23,24] The AHA/ACC/ESC guidelines for the management of ventricular arrhythmias and the prevention of SCD[7] indicate that therapy with amiodarone or sotalol has been shown to reduce the frequency of ICD shocks and recommend therapy with sotalol or, alternatively, the combination of β-blockers and amiodarone, for the management of patients with ICDs who have recurrent ventricular tachycardia (VT)/ventricular fibrillation (VF) with frequent appropriate ICD firing. Similarly, these guidelines recommend therapy with β-blockers and/or calcium channel antagonists for the management of patients with ICDs who have paroxysmal or permanent atrial fibrillation (AF) with rapid ventricular rates, who, in turn, receive inappropriate ICD firing; amiodarone is recommended for this patient population if β-blockers and/or calcium channel antagonists are contraindicated, poorly tolerated or ineffective.[7] Therefore, the administration of antiarrhythmic drugs to patients with ICDs is not uncommon.

There are specific indications for concomitant non-antiarrhythmic drug therapy in patients with devices that combine a biventricular pacemaker and an ICD. Patients must be receiving optimal medical therapy for treatment of heart failure, including ACE inhibitors, angiotensin II receptor antagonists, β-blockers and aldosterone antagonists when indicated, and diuretics and digoxin for symptom relief. All trials showing morbidity and mortality benefits with implantable devices have required patients to be on a stable regimen of these agents, usually meaning at least 1 month of ACE inhibitor therapy and 3 months of β-blocker therapy.[18-20] This hybrid of device and drug therapies results in improvements in LVEF, NYHA class and symptoms, and enhanced tolerability of further up-titration of drug doses toward targets.

2. Methods of Literature Review

Multiple search strategies were used for this review. The MEDLINE database was searched from 1966 to December 2007. Keywords were as follows: antiarrhythmic drugs; cardiovascular drugs; amiodarone; sotalol; flecainide; propafenone; dofetilide; ibutilide; β-blockers; lidocaine; procainamide; N-acetylprocainamide; mexiletine; disopyramide; moricizine; calcium channel blockers; defibrillation threshold; defibrillation energy requirements; defibrillation energy changes; defibrillation efficacy; implantable cardioverter defibrillators; and external defibrillators. Combinations of these terms filtered the journal articles that specifically studied drug effects of defibrillation energy. Reference lists from review articles that were identified using the search strategy were also searched to identify pertinent articles.

The strength of evidence regarding the effects of specific drugs on defibrillation capacity was classified as level A, B or C (table I).[3,7] In cases for which the only available data are derived from animal studies, a level of evidence was not assigned.

Table I. Levels of evidence[3,7]

Level of evidence	
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized trial or nonrandomized studies
C	Only consensus opinion of experts, case studies or standard-of-care

3. Drugs and Defibrillation Capacity

3.1 Defibrillation Threshold

Defibrillation threshold (DFT) is defined as the lowest amount of energy required to successfully defibrillate the heart and restore normal sinus rhythm. The defibrillation energy output of ICDs ranges between 25 and 35 J, depending on the device manufacturer. During ICD implantation, VF is induced, most frequently by strategically delivering a 1-J shock from the implanted device during the T wave or elsewhere during the repolarization phase of the ventricle. Subsequently, the ICD is programmed to deliver up to two defibrillation shocks in an attempt to successfully defibrillate the fibrillating heart. If the ICD fails to produce successful defibrillation, external defibrillation shocks are delivered through external pads that are placed during preparation for the procedure. The goal of the induction is to ensure that an adequate safety margin (10 J) exists between the DFT of the patient and the maximum output of the device. Optimal determination of DFT includes construction of a continuous dose-response curve between the energy delivered and the success of the defibrillation shock. However, because of the time required for multiple inductions of VF and subsequent defibrillation attempts, this entire process is not performed clinically. Rather, two methods have been used in clinical practice: a step down to failure method and a binary search method. The latter requires fewer inductions and shocks, and is comparable in efficacy.[25] Many electrophysiologists simply programme the device to deliver a shock of 10 J less than the maximum output of the device and, if this successfully defibrillates, do not attempt to further refine the actual DFT measurement.

Vulnerability, as it relates to defibrillation energy and thresholds, is under study as a method of assessment of defibrillator output. The upper limit of vulnerability (ULV) is defined as the strength (in joules) at or above a level at which VF cannot be induced when a stimulus is delivered during the refractory (vulnerable) phase of a cardiac cycle.[26] The ULV has been studied as a predictor of DFT as a means of reducing the number of VF inductions, which are time consuming and potentially dangerous to the patient.[26-28] The ULV method delivers a shock of 10–15 J on or near the peak of the T wave. The weakest shock strength that fails to induce VF is defined as the ULV of the patient.[28,29] Several studies have established a correlation between the ULV and DFT.[26-28] This method is not yet used widely in clinical practice; however, some studies have used the ULV for determining the potential interaction between antiarrhythmic drugs and the success of defibrillation.

3.2 Biphasic versus Monophasic Shocks

Traditionally, defibrillation shocks were monophasic, where the energy is delivered in one direction (i.e. in a constant polarity). However, it is now well established that defibrillation shocks are more effective if delivered in a biphasic manner, where the polarity is reversed midway through the shock.[30,31]

3.3 Mechanisms of Effects of Drugs on Defibrillation Capacity

Defibrillation efficacy may be influenced by a number of factors, including inhibition of conductance through ion channels (i.e. sodium, potassium),[32-40] plasma electrolyte concentrations,[32] neurohormonal modulation,[41-48] gap junction inhibition[49] and intravascular volume status.[50]

Evidence indicates that prolongation of cardiac repolarization via inhibition of potassium conductance reduces DFT.[32,33] In a study of pentobarbital-anaesthetized dogs receiving intravenous potassium chloride, Babbs et al.[32] demonstrated a linear relationship between the percentage decrease in DFT, and the logarithm of extracellular plasma potassium concentration and the potassium equilibration potential, calculated from measured extracellular and intracellular (ventricular myocyte) potassium concentrations. Ujhelyi et al.[33] reported that prolongation of ventricular repolarization through inhibition of outward potassium conductance with caesium chloride significantly decreased DFT values. Combined inhibition of the potassium channels I_{Kr} and

I_{K1} does not produce additive effects on lowering DFT compared with inhibition of either channel individually.[34] Similarly, combined inhibition of I_{Kr} and I_{Ks} channels does not produce a greater degree of reduction in DFT compared with that associated with I_{Kr} channel blockade alone.[35] However, inhibition of potassium-adenosine triphosphate channels has no effect on DFT values.[36]

In contrast to potassium channel inhibition, sodium channel blockade significantly increases DFT with monophasic shocks, but not with biphasic shocks,[37] as a result of differential effects on the area of vulnerability and the ULV associated with monophasic (but not biphasic) shocks.[38,39] However, sodium channel inhibition-induced elevations in DFT are attenuated in the presence of concomitant potassium channel blockade.[33]

Modulation of intracellular calcium concentrations also influences defibrillation. Zaugg et al.[40] demonstrated that increasing intracellular calcium concentrations from 3 to 6 mmol/L resulted in an increase in DFT from 1.9 ± 0.6 to 3.5 ± 1.5 J/g in isolated perfused rat hearts. Termination of VF occurred with greater frequency in isolated rat hearts perfused with a low calcium concentration perfusate or through calcium channel inhibition with a perfusate containing amiodarone than with a control perfusate.[41] Reduction of intracellular calcium concentrations via inhibition of the Na^+/Ca^{2+} exchanger with flunarizine was shown to significantly reduce DFT values.[42]

Some evidence indicates that neurohormonal modulation may influence defibrillation efficacy, although data are somewhat conflicting. In an anaesthetized pig model, phenylephrine infusion significantly reduced DFT (determined by a sequential pulse method) from 10.2 ± 0.65 to 8.9 ± 0.89 J.[43] Sequential-pulse DFT was not significantly altered by infusions of phentolamine or isoprenaline (isoproterenol); however, isoprenaline infusion significantly reduced DFT (from 17.3 ± 1.5 to 14.6 ± 1.9 J) when determined using a single-pulse method.[43] Sezaki et al.[44] found that isoprenaline had no effect on ventricular DFT in anaesthetized dogs. In addition, isoprenaline did not antagonize (or facilitate) the effects on DFT of the potassium channel inhibitor E-4031. Modulation of sympathetic tone using infusions of phenylephrine or isoprenaline exerted no significant effect on atrial DFT in patients undergoing radiofrequency ablation of supraventricular tachycardia; the combination of phenylephrine and atropine similarly produced no effect on atrial DFT in these patients.[45] Kalus et al.[46] reported that infusion of norepinephrine (noradrenaline) resulted in a significant reduction in DFT in patients with ICDs. The influence of norepinephrine on DFT was independent of β-blocker use. Epinephrine (adrenaline) infusion had no significant effect on DFT; subgroup analysis suggested that epinephrine reduced DFT in patients receiving β-blockers but, conversely, increased DFT in patients not receiving β-blockers. Animal data also suggest that epinephrine may increase DFT.[47] While further data regarding the influence of modulation of the autonomic nervous system on DFT are required, these data suggest that stimulation of α_1 receptors results in reductions in DFT, and stimulation of β_1 receptors has minimal influence on DFT.

Other neurohormonal systems may influence DFT. Murakawa et al.[48] studied the effects of atrial natriuretic peptide (ANP) on DFT in anaesthetized dogs. Administration of ANP resulted in a significant reduction in ventricular DFT (from 5.4 ± 1.2 to 3.8 ± 0.7 J). Administration of hydralazine exerted no significant influence on DFT, suggesting that the effects of ANP are related to effects other than vasodilation, such as elevation of plasma concentrations of cyclic guanosine monophosphate.[48]

Gap junction modulation may affect DFT. Qi et al.[49] reported the effects of administration of the gap junction blockers 16-deoxyl-stearic acid (16-DSA) and *1*-heptanol on DFT in isolated perfused rabbit hearts. Both 16-DSA and *1*-heptanol significantly decreased DFT (by 23% ± 14% and 21% ± 16%, respectively). The investigators reported that these gap junction-blocking agents exerted no significant effect on ventricular effective refractory period or monophasic action potential duration. However, gap junction inhibition significantly influ-

Table II. Influence of specific drugs on defibrillation threshold (DFT); data obtained from clinical studies and/or case reports

Drug	Ventricular DFT		Atrial DFT	
	effect	level of evidence	effect	level of evidence
Amiodarone	↑ (monophasic) ↑ (biphasic)	B B	ND	
Sotalol	↓ (monophasic) ↔ (biphasic)	B B	ND	
Flecainide	ND		↓	B
Propafenone	↔	B	ND	
Lidocaine	↑	C	ND	
Procainamide	↔	C	ND	
Acecainide	ND		ND	
Ibutilide	ND		↓	B
Disopyramide	ND		ND	
Dofetilide	ND	ND	ND	
Mexiletine	↑	C	ND	
Moracizine	↑	C	ND	
β-Blockers	↓	B	ND	
Verapamil	↑	C	ND	
Digoxin	ND		ND	
Venlafaxine	↑	C	ND	
Anaesthetic agents	↑	C	ND	

ND = no data; ↑ indicates increases; ↓ indicates decreases; ↔ indicates no effect.

enced VF organization, as indicated by reduced dispersion of ventricular fibrillation cycle length; the investigators suggest this as a mechanism by which gap junction inhibition may reduce DFT.[49]

The influence of acute volume overload on ventricular DFT was investigated in a canine noradrenaline-infusion model of tachycardia (by rapid pacing)-induced LVD, resulting in LVEF <35%.[50] Normal saline was infused to achieve a pulmonary capillary wedge pressure >19 mmHg. Induction of LVD in the absence of acute volume overload did not significantly alter DFT compared with baseline values; however, in the presence of LVD and acute volume overload, ventricular DFT increased from 3.3 ± 2.0 to 6.4 ± 2.5 J ($p < 0.02$).

4. Effects of Specific Drugs on Defibrillation Capacity

A summary of the effects of specific drugs on DFT is shown in table II. Amiodarone and sotalol are discussed first as they are used in clinical practice more frequently, followed by antiarrhythmic drugs, cardiovascular drugs and non-cardiovascular drugs.

4.1 Amiodarone

4.1.1 Animal and Ex Vivo Studies

The effects of amiodarone on ventricular DFTs in animal models have produced conflicting results. The effects of long-term therapy with oral amiodarone (50 mg/kg/day for 28 days) on ventricular DFT (n = 10) did not result in a significant difference in monophasic or biphasic DFT compared with that in a control group (n = 10) in an isolated perfused heart model.[51] Intravenous amiodarone administered as a 10-mg/kg dose to dogs (n = 12) resulted in a decline in ventricular DFT by 22 ± 12%; however, amiodarone administered orally (300 or 400 mg/day) resulted in no significant change in DFT.[52,53] In contrast, intravenous amiodarone administered as the same dose, 10 mg/kg, produced an elevation in ventricular DFT of 32%.[39] In another study,[54] three groups of six healthy dogs received oral amiodarone 200 mg/day for 9 days, 400 mg/day for 9 days or no drug. Intravenous ami-

odarone 5 mg/kg was administered as a single dose to five dogs, each of which served as its own control. After 9 days of therapy, DFT was significantly higher in animals receiving amiodarone 200 and 400 mg/day compared with those in the control group (15.4 ± 5.4 and 17.9 ± 7.4 vs 7.5 ± 2.9 J, respectively).[54] In contrast, amiodarone administered intravenously as a single dose did not result in a significant elevation in DFT compared with pretreatment values (10.8 ± 1.4 vs 10.8 ± 1.8 J). In a pig model of regional coronary ischaemia, intravenous amiodarone 5 mg/kg (n = 10) resulted in no significant difference in DFT compared with a group of control animals (n = 5) that received normal saline.[55] Huang et al.[56] randomized two groups of dogs (each n = 12) to receive therapy with amiodarone or placebo (saline). In one group, animals were randomized to receive acute intravenous amiodarone 10 mg/kg or placebo; in the other group, animals were randomized to receive long-term oral amiodarone (20 mg/kg/day) or placebo for 30 days. Neither acute nor long-term amiodarone therapy resulted in significant changes in biphasic DFT compared with placebo.

Reasons for these disparate findings are unclear. It is possible that differences in results could be explained, in part, by the duration of VF prior to defibrillation;[51] in studies where DFT was unchanged or reduced in association with amiodarone, time in VF was shorter (5–20 seconds),[51,52,56] in comparison with 20–80 seconds in one of the studies where DFT was elevated in association with oral amiodarone.[57]

4.1.2 Case Reports

Fogoros[58] reported the case of a 56-year-old man with a history of four myocardial infarctions, two coronary artery bypass graft procedures, and recurrent ventricular tachyarrhythmias for which an ICD was implanted following 65 days of therapy with oral amiodarone. During testing of the device immediately following implantation, induced ventricular flutter was not successfully terminated by a 20-J discharge of the ICD, but rather the rhythm degenerated into VF. A subsequent 40-J discharge failed to terminate the VF. The arrhythmia was terminated, and sinus rhythm restored, following three 400-J external defibrillation shocks. Therapy with amiodarone was discontinued, and 3 months later, the patient was readmitted for ICD testing. Induced ventricular flutter was successfully terminated with one 25-J ICD discharge. The DFT was determined to be 10 J. The author concluded that refractoriness to defibrillation occurred as a result of therapy with oral amiodarone.

A 27-year-old man underwent ICD implantation for the management of monomorphic VT refractory to therapy with β-blockers and quinidine.[59] Prior to ICD placement, he received 78 days of therapy with oral amiodarone; during most of this period, the amiodarone dose was 800 mg/day. During ICD testing, DFT was 35–40 J. Eight days after ICD implantation, amiodarone therapy was discontinued. Seventy-one days following discontinuation of amiodarone therapy, the DFT had declined to 20 J.

Boriani et al.[60] described the case of a 57-year-old man with idiopathic dilated cardiomyopathy (LVEF 30%) who underwent therapy with oral amiodarone (200 mg/day) for 6 months for the management of sustained VT. Despite amiodarone therapy, the arrhythmia was inducible during an electrophysiology study and the patient underwent ICD implantation. ICD shocks of 16, 22.8 and 27 J were ineffective for defibrillation of induced VF; only maximal shocks at 36 J were effective. The ICD was programmed at maximal output (36 J) and oral amiodarone therapy was discontinued. Forty days after discontinuation of amiodarone therapy, *d,l*-sotalol was initiated and the dose was titrated to 320 mg/day. Two weeks later, defibrillation testing was performed and ICD shocks of 23.8 J were effective for termination of induced VF. In a similar case reported by the same authors,[61] a 29-year-old man with hypertrophic nonobstructive cardiomyopathy underwent ICD implantation for nonsustained VT. At the time of implantation, the patient had been receiving therapy with oral amiodarone 1000 mg/week for 3 years. During testing of the ICD, biphasic DFT was greater than 36 J and the patient required external defibrillation. Amiodarone therapy was discontinued. Two months later, therapy was initiated with

sotalol 360 mg/day. DFT testing during sotalol therapy demonstrated successful defibrillation of induced VF with an ICD shock of 24 J.

4.1.3 Clinical Studies

The effects of amiodarone therapy on DFT have been determined in several studies. Kühlkamp et al.[62] performed a retrospective analysis of drug effects on DFT in 89 patients in whom an ICD was implanted; in 18 patients, the ICD delivered monophasic shocks, and in 71 patients, biphasic shock devices were used. DFTs were determined using a consistent step-down protocol. Of the 18 patients with a monophasic ICD, 7 were receiving long-term therapy with oral amiodarone, while 11 received no antiarrhythmic therapy. Of the 71 patients with a biphasic ICD, 29 were receiving long-term therapy with amiodarone, 20 underwent long-term sotalol therapy and 22 were receiving no antiarrhythmic therapy. In patients with an ICD that delivered monophasic shocks, DFT was significantly higher in patients receiving long-term amiodarone therapy (29.1 ± 8.8 J), compared with those on no antiarrhythmic therapy (19.1 ± 5.1 J; p = 0.021). In contrast, in patients with a biphasic device, there was no significant difference in DFT in those receiving long-term amiodarone, sotalol or no antiarrhythmic drug treatment (15.3 ± 7.3, 14.4 ± 7.2 and 17.0 ± 6.1 J, respectively).

In a prospective, observational study in 22 patients with early-generation ICDs, DFT was evaluated at the time of ICD implantation and generator replacement (mean follow-up 24 ± 6 months).[63] Mean DFT increased from 14.1 ± 3.0 to 20.9 ± 5.4 J (p < 0.001) in patients receiving amiodarone 400 mg/day. There was no significant change in DFT in patients receiving therapy with mexiletine 720 mg/day. Amiodarone therapy was the only variable that was independently associated with elevation in DFT; in all patients who developed increases in DFT, values returned to baseline following drug discontinuation. A study of 42 defibrillation lead systems in 41 patients with ICDs, therapy with amiodarone was again the only variable that was independently associated with elevations in DFT.[64] Similarly, treatment with oral amiodarone was significantly associated with higher DFTs in a retrospective analysis of 365 patients with ICDs.[65] In contrast, in a study of 101 patients, there was no significant difference in mean DFT between patients who had undergone 'recent' amiodarone therapy compared with those who had not.[66]

Daoud et al.[67] prospectively evaluated 102 patients who underwent ICD implantation, of whom 40 received oral amiodarone within 48 hours of ICD placement. In 19 of these patients, oral amiodarone loading (1800 mg/day for 10 days) was performed acutely; in 21 patients, the mean duration of oral amiodarone therapy was 7 ± 6 months. The mean DFT in patients receiving amiodarone was significantly higher than that in those not receiving the drug (22 ± 10 vs 17 ± 9 J; p = 0.01). There was no significant correlation between plasma amiodarone or desethylamiodarone concentration and DFT.

The OPTIC (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients) trial was a randomized study in which the efficacy of β-blockers, amiodarone combined with β-blockers, or sotalol for the prevention of shocks was compared in 412 patients with ICDs.[68] The results of this study suggested that combination therapy with amiodarone and β-blockers was more effective than sotalol or β-blockers alone for reducing the incidence of shocks, but was associated with a higher incidence of adverse effects. In a prospectively designed substudy of OPTIC, the effects of amiodarone combined with β-blockers versus sotalol or β-blockers alone on DFT were determined in 94 patients in whom DFT was measured prior to and 8–12 weeks after the initiation of drug therapy.[2,68] All patients enrolled in OPTIC underwent pectoral implantation of a specific biphasic shock-capable, dual-chamber, 'active can' ICD. Patients randomized to receive β-blockers (with or without amiodarone) were given metoprolol, carvedilol or bisoprolol. In patients randomized to β-blockers alone, DFT decreased from 8.77 ± 5.15 to 7.13 ± 3.43 J (p = 0.027). Sotalol therapy provoked no significant change in DFT (8.09 ± 4.81 J at baseline vs 7.20 ± 5.30 J during therapy; p = 0.21). In patients receiving combined therapy with amiodarone

and β-blockers, there was a trend towards an increase in DFT (from 8.53 ± 4.29 to 9.82 ± 5.84 J; p = 0.091). The change in mean DFT in the β-blocker group (which decreased from baseline) compared with that in the combined amiodarone plus β-blockers group (which was nonsignificantly increased from baseline) was significantly different (p = 0.006). Similarly, the mean change in DFT in the combined amiodarone plus β-blockers group was significantly different from that in the sotalol group (p = 0.038). The investigators concluded that, although the change in mean DFT associated with the combination of amiodarone and β-blockers was significantly greater than that seen in patients treated with β-blockers alone, the magnitude of difference was sufficiently small as to be clinically insignificant, and they recommended that routine assessment of DFT in patients receiving therapy with amiodarone is not necessary.[2]

Leong-Sit et al.[69] performed a retrospective evaluation of the records of 168 patients who underwent ICD implantation between 1999 and 2003, for the purpose of determining clinical and echocardiographic predictors of the need for DFT testing. Amiodarone use was an independent risk factor for defibrillation failure (odds ratio 4.56; 95% CI 1.22, 17.0). In addition, patients receiving therapy with amiodarone had mean DFT (or lowest energy to defibrillate) values that were 1.36 J higher than those in patients not receiving amiodarone therapy (p = 0.004). The proportion of patients also receiving therapy with β-blockers is not provided; however, based on the characteristics of the patient population (ischaemic heart disease 63%, nonischaemic dilated cardiomyopathy 15%), it seems likely that many patients in this study were receiving therapy with β-blockers. Based on these findings, the authors recommend that DFT testing remain a component of standard ICD implantation, particularly in patients receiving therapy with amiodarone.

4.1.4 Summary

Data regarding the effects of amiodarone on DFT are conflicting. Some published cases indicate that, in some patients, amiodarone therapy may elevate DFT. However, data from clinical trials suggest that these effects primarily pertain to ICDs that deliver monophasic shocks, and that the potential for an interaction between amiodarone and ICDs that deliver biphasic shocks is substantially lower. Based on the findings of Leong-Sit et al.,[69] initial DFT testing should be performed in patients who undergo ICD implantation while receiving therapy with amiodarone. However, subsequent routine assessment of DFT in patients who continue to receive therapy with amiodarone may not be required. (Level of evidence: B.)

4.2 Sotalol

4.2.1 Animal Studies

The effects of intravenous *d,l*- and *d*-sotalol on ventricular DFT were studied in dogs anaesthetized with pentobarbital (n = 18) or fentanyl (n = 18).[70] Compared with placebo (saline), *d,l*- and *d*-sotalol decreased DFT by 16% ± 14% (p < 0.05) and 25% ± 8% (p < 0.05), respectively, in fentanyl-anaesthetized animals. In dogs anaesthetized with pentobarbital, *d,l*-sotalol did not significantly influence DFT, whereas *d*-sotalol reduced DFT by 11% ± 16% (p < 0.05).

Iskos et al.[71] studied the effects of intravenous *d*-sotalol on atrial DFT in an anaesthetized canine model of AF (n = 7). *d*-Sotalol 5 mg/kg decreased atrial DFT from 1.72 ± 1.12 to 0.59 ± 0.60 J (p < 0.05).

4.2.2 Case Reports

In two cases described in section 4.1.2,[60,72] therapy with sotalol was initiated in patients with high DFTs while receiving therapy with amiodarone. In both cases, DFT declined significantly following the discontinuation of amiodarone and initiation of therapy with sotalol.

4.2.3 Clinical Studies

In a prospective study in 15 patients undergoing ICD implantation, ventricular DFT was determined prior to and 20 minutes after the initiation of an infusion of *d*-sotalol (2 mg/kg infused over 15 minutes, followed by 1 mg/kg/h).[73] *d*-Sotalol was associated with a reduction in ventricular monophasic

DFT (from 12.4 ± 5.0 to 8.4 ± 4.0 J; $p < 0.003$). In addition, *d*-sotalol produced a decrease in the voltage required for 50% successful defibrillation (ED_{50}) from 440 ± 77 to 354 ± 93 V; $p < 0.001$.[73] In a retrospective study of 71 patients with implanted ICDs capable of delivering biphasic shocks, there was no significant difference in DFT in patients receiving long-term therapy with amiodarone, sotalol or no antiarrhythmic drugs.[62] Dorian and Newman[74] reported that, in a retrospective analysis of patients with ICDs, ventricular DFT in those receiving therapy with oral sotalol (n = 25) was lower than that in a comparison group of 23 patients, 18 of whom were receiving oral amiodarone (5.9 ± 3.4 vs 16.0 ± 10.0 J; $p < 0.01$).

The effects of sotalol on atrial DFT were investigated in 25 patients with refractory AF; 13 patients had acute AF, 12 had chronic AF.[75] Transvenous atrial defibrillation was performed using biphasic shocks and atrial DFT was measured. In patients in whom sinus rhythm was restored for >1 minute (all patients with acute AF; n = 9 in patients with chronic AF), intravenous sotalol 1.5 mg/kg was administered over a period of 15 minutes, after which AF was re-induced via rapid atrial pacing, followed by atrial defibrillation and determination of atrial DFT. In patients with acute AF, sotalol reduced the atrial DFT from 1.5 ± 1.0 to 0.9 ± 0.5 J ($p < 0.05$). In patients with chronic AF, sotalol had no significant influence on atrial DFT.[75]

In the subgroup analysis of the OPTIC study,[2] sotalol therapy had no significant effect on ventricular DFT in patients with ICDs (active pectoral lead systems) that deliver biphasic shocks.

4.2.4 Summary

Available data suggest that *d*-sotalol and *d,l*-sotalol may reduce ventricular DFT and that *d,l*-sotalol may reduce atrial DFT. In patients with ICDs that deliver biphasic shocks, sotalol has no effect on DFT[2] and routine monitoring of DFT in this population is not necessary. (Level of evidence: B.)

4.3 Flecainide

4.3.1 Animal Studies

Studies of the effects of flecainide on DFT in animal studies have yielded conflicting results. Szabo et al.[76] studied the effects of flecainide on ventricular DFT, measured by sequential pulse defibrillation, in pigs anaesthetized with ketamine and diazepam. The animals were divided into four groups: subtherapeutic (0.04 mg/kg bolus followed by 0.06 mg/kg/h, n = 6); therapeutic (0.45 mg/kg bolus followed by 0.60 mg/kg/h, n = 8); supratherapeutic (1.80 mg/kg bolus followed by 2.4 mg/kg/h, n = 8); and placebo (n = 5). Compared with placebo, flecainide did not significantly alter ventricular DFT at any of the tested doses. Similarly, Natale et al.[77] reported that administration of low, medium or high doses of intravenous flecainide had no significant effect on DFT in pigs, regardless of the type of anaesthesia employed (pentobarbital vs halothane). In contrast, flecainide administered by continuous intravenous infusion increased the ED_{50} from a pretreatment value of 6.5 ± 1.9 to 11.4 ± 2.6 J ($p < 0.05$) in ten anaesthetized dogs.[78] In another study, VF was rendered refractory to defibrillation in two of five dogs that received intravenous flecainide.[79] Flecainide was shown to increase DFT from 4.2 ± 1.3 to 6.1 ± 1.5 J ($p < 0.005$) in nine anaesthetized dogs.[80]

4.3.2 Clinical Studies

Boriani et al.[81] investigated the effects of flecainide on atrial defibrillation requirements in 19 patients with persistent AF and in five patients with paroxysmal AF undergoing elective transvenous cardioversion. Atrial fibrillation was converted to sinus rhythm prior to drug administration, after which AF was re-induced by atrial pacing. Flecainide 2 mg/kg was administered intravenously and conversion of AF to sinus rhythm was repeated. In patients with persistent AF, flecainide decreased atrial DFT from 4.42 ± 1.37 to 3.50 ± 1.15 J ($p < 0.005$). Similarly, in patients with paroxysmal AF, flecainide reduced atrial DFT from 1.68 ± 0.29 to 0.84 ± 0.26 J ($p < 0.01$).

4.3.3 Summary

Clinical data regarding the effects of flecainide on ventricular DFT are lacking. Data from animals regarding the effect of flecainide on ventricular DFT are conflicting, but some evidence suggests that flecainide may increase DFT. Clinical data indicate that flecainide may have a favourable effect on atrial defibrillation by reducing atrial DFT. (Level of evidence: B.)

4.4 Propafenone

4.4.1 Animal Studies

Studies of the effects of propafenone on ventricular DFT have produced conflicting results. Intravenous propafenone (2 mg/kg bolus, followed by 1 mg/min [n = 2] or 25 μg/kg/min [n = 8]) was reported to increase epicardial DFT in ten dogs anaesthetized with pentobarbital.[82] DFT was determined using the step-down procedure. The ED_{50} increased during propafenone administration compared with the pretreatment value (14.7 ± 5.9 vs 8.4 ± 2.4 J; $p < 0.05$). Similarly, the energy at 80% successful defibrillation (ED_{80}) increased during propafenone administration compared with pretreatment measurements (17.6 ± 6.7 vs 11.1 ± 3.5 J; $p < 0.05$).

In contrast, propafenone has also been reported to decrease ventricular DFT. Natale et al.[83] studied the effects of acute and prolonged administration of propafenone on epicardial DFT in 43 pigs anaesthetized with a mixture of ketamine and diazepam. Animals were assigned randomly to receive intravenous saline infusion (n = 10), propafenone infusion (0.04 mg/kg/min for 40 minutes, followed by 0.1026 mg/kg/min, n = 10), long-term administration of placebo (n = 10) or long-term administration of propafenone (2 mg/kg twice daily for 8 days, n = 13). Intravenous propafenone decreased DFT from 20 ± 6.2 to 15.6 ± 5.0 J at 40 minutes ($p < 0.05$) and 10.2 ± 6.0 J at 80 minutes ($p < 0.001$). Similarly, long-term therapy with propafenone reduced DFT from 17.8 ± 2.6 to 12.0 ± 3.2 J ($p < 0.002$). DFT was unchanged in the placebo groups. Similar results were reported in a study of 20 anaesthetized pigs, half of which received placebo and the other half received a continuous infusion of propafenone 0.04 mg/kg.[84] Propafenone reduced the DFT from 20 ± 7 to 9 ± 6 J ($p < 0.001$); there was no significant change in DFT in the placebo group. Reasons for the disparate findings in these studies are unclear. Plasma propafenone concentrations were similar in two of the studies with conflicting findings.[82,83] The animal models and the methods of determination of DFT were different, as were the anaesthetic agents used, and it is possible that these differences contributed to the incongruent findings.

4.4.2 Clinical Studies

The effects of oral propafenone on DFT were investigated in a randomized, double-blind, three-way parallel study.[85] Following ICD implantation and baseline DFT measurement, 47 patients were randomized to receive propafenone 150 mg three times daily (group 1, n = 15), propafenone 225 mg three times daily (group 2, n = 14) or placebo (group 3, n = 18) for 3–7 days during hospitalization. Repeat measurement of DFTs was performed prior to discharge. There were no significant differences between groups 1, 2 or 3 in pre-propafenone DFTs (11.0 ± 1.3 vs 11.5 ± 1.1 vs 12.5 ± 1.2 J). Similarly, there were no significant differences between the groups in on-treatment DFTs (12.1 ± 1.5 vs 13.6 ± 1.3 vs 13.3 ± 1.6 J). The results of the study were not different in an analysis of patients with LVEF ≤30% versus those with LVEF >30%.

4.4.3 Summary

Short-term administration of oral propafenone does not influence DFT in humans. (Level of evidence: B.) The effects of longer-term administration of oral propafenone on DFT have not been evaluated in humans and remain uncertain.

4.5 Lidocaine

4.5.1 Animal and *Ex Vivo* Studies

The effects of escalating concentrations of lidocaine on ventricular DFT were studied in isolated perfused rabbit hearts.[86] In this study, ED_{50} and ED_{80} were determined prior to drug administration, and during increasing concentrations of lidocaine (1.5, 2.0 and 3.0 μg/mL). Compared with baseline,

lidocaine at these three concentrations increased ED_{50} 146%, 223% and 312%, and increased ED_{80} 139%, 207% and 285%, respectively.[86]

In a study of pentobarbital-anaesthetized dogs, intravenous lidocaine produced an elevation in ventricular DFT of 50–100%.[87] In another study of pentobarbital-anaesthetized dogs,[88] lidocaine increased DFT (defined as the 90% effective energy dose) from 11 ± 5 to 24 ± 12 J ($p < 0.05$). In chloralose-anaesthetized dogs undergoing closed chest cardiopulmonary resuscitation, intravenous lidocaine 2 mg/kg resulted in an increase in ventricular DFT compared with that in a control group (53.0 ± 40.7 vs 34.3 ± 30.7 J; $p < 0.05$).[89] Lidocaine increased DFT by 27% in pentobarbital-anaesthetized pigs.[90] The combination of lidocaine and moracizine significantly increased DFT compared with that associated with moracizine alone. Lidocaine was shown to increase DFT in dogs pretreated with flecainide.[91]

Kerber et al.[92] found that the effect of intravenous lidocaine on ventricular DFT in dogs was dependent on the type of anaesthetic administered. In dogs anaesthetized with pentobarbital, DFT increased by up to 60%; however, in chloralose-anaesthetized dogs, lidocaine was not associated with a significant change in DFT. Similarly, Natale et al.[93] reported that lidocaine increased ventricular DFT in pigs anaesthetized with pentobarbital, but that lidocaine had no effect on DFT in pigs anaesthetized with halothane. In a study of 11 open-chest dogs anaesthetized with pentobarbital,[94] intravenous lidocaine (n = 7) increased ventricular DFT from 4.4 ± 1.1 to 8.7 ± 1.7 J ($p = 0.01$). Additional data indicate that the effect of lidocaine on DFT is dependent on the defibrillation electrode system studied; in a study in pigs, lidocaine increased DFT by 59% in animals defibrillated using epicardial electrodes, but only 16% in animals defibrillated using endocardial leads.[95] These data suggest that the effect of lidocaine on DFT in humans in whom endocardial defibrillation leads are placed may be of minimal clinical significance.

4.5.2 Case Reports

A 59-year-old man with coronary artery disease and heart failure due to LVD underwent ICD implantation for the management of inducible sustained monomorphic VT.[96] Following the ICD implantation, the initial DFT was 15 J. For purposes of creating the subcutaneous pulse generator pocket, anaesthesia was induced briefly with intravenous propofol 200 mg and lidocaine 100 mg (10 mL of a 1% solution). During subsequent testing of the device, defibrillation using a 30-J biphasic shock was unsuccessful, necessitating the administration of a 34-J 'rescue' shock for restoration of sinus rhythm. The serum lidocaine concentration 30 minutes after the 100-mg dose was 3.8 μg/mL. DFT was tested again 30 minutes later, revealing a DFT of 10 J. The authors concluded that DFT was transiently elevated as a result of the administration of lidocaine.[96]

4.5.3 Clinical Studies

The effects of lidocaine on DFT were assessed in eight patients undergoing arrhythmia surgery for Wolff-Parkinson-White syndrome.[97] Following electrophysiological mapping of the accessory conduction pathway, three coiled defibrillation electrodes were attached to the left and right ventricular epicardium. VF was induced using alternating current; after a minimum of 10 seconds of VF, DFT was determined using sequential pulses. Following the measurement of pretreatment DFTs, intravenous lidocaine was administered at a dose of 150 mg over less than 30 seconds. DFT was determined again 5 minutes after lidocaine administration. Pretreatment DFT and post-lidocaine DFT were not significantly different (3.0 ± 1.4 vs 3.0 ± 1.8 J).

4.5.4 Summary

Available data suggest that the effects of lidocaine on ventricular DFT in humans with endocardial ICD leads may be minimal. However, in view of the case described in section 4.5.2,[96] it appears possible that hospitalized patients receiving therapy with intravenous lidocaine may require greater defibrillation energy for restoration of sinus rhythm. (Level of evidence: C.)

4.6 Procainamide

4.6.1 Animal Studies

Procainamide administered as a single dose of 15 mg/kg resulted in no significant change in DFT from baseline in a study of dogs (n = 6) and pigs (n = 6).[98] DFT was also not significantly altered by the administration of procainamide 20 mg/kg over 30 minutes, followed by a continuous infusion of 2 mg/kg/min in six pentobarbital-anaesthetized dogs.[99] Further, procainamide had no effect on DFT, despite achievement of therapeutic plasma concentrations, in another study conducted in pentobarbital-anaesthetized dogs.[88]

4.6.2 Case Reports

A 78-year-old man with a history of myocardial infarction underwent ICD implantation for treatment of inducible sustained monomorphic VT.[100] One month after ICD implantation, therapy was initiated with oral sustained-release procainamide at a dose of 500 mg three times daily for the management of frequent inappropriate shocks. One month later, he experienced several ICD shocks for sustained VT. During electrophysiology studies, induced VT could not be terminated using shocks of 30 J, but was consistently converted to sinus rhythm using lower energy shocks (6 J). The authors attributed this unusual finding to a previously unreported effect or idiosyncratic reaction to procainamide. However, procainamide therapy did not alter the DFT in this patient; the DFT remained at the pre-procainamide value of 14 J during treatment with the drug.[100]

4.6.3 Summary

Procainamide has minimal or no effect on ventricular DFT. (Level of evidence: C.)

4.7 Acecainide

The active metabolite of procainamide, acecainide or N-acetyl procainamide, exhibits substantially different electrophysiological effects from those of the parent drug; acecainide primarily prolongs ventricular action potential duration via prolongation of phase 3 repolarization.[101] Through hepatic acetylation of procainamide, acecainide is present in physiologically relevant concentrations in individuals receiving therapy with procainamide.[72]

4.7.1 Animal Studies

Acecainide significantly reduced the DFT from 15 ± 5 to 10 ± 2 J in a study of dogs anaesthetized with pentobarbital.[88]

4.7.2 Summary

Data from a single dog study indicate that acecainide is associated with a significant reduction in DFT. Case reports or studies including humans have not been published.

4.8 Ibutilide

4.8.1 Animal Studies

In a study of pentobarbital-anaesthetized dogs,[102] the effects of ibutilide on ventricular DFT were investigated using two methods of DFT determination. In protocol I, a decremental shock protocol was used for determination of baseline DFT, and an incremental shock protocol was used to determine the effects of intravenous ibutilide 0.1 mg/kg (n = 9) or placebo (n = 3) on DFT. Ibutilide reduced DFT by 42%, from 27.7 ± 17.7 to 16.0 ± 11.9 J (p = 0.002). Administration of placebo (normal saline) resulted in no change in DFT. In protocol II, a DFT shock 'dose-response' method was used to determine the effects of ibutilide (n = 6) administered as an intravenous bolus (0.075 mg/kg) followed by a continuous infusion (0.00125 mg/kg/min) or placebo (n = 5) on DFT. The shock 'dose' associated with 50% successful defibrillation was shifted from 14.8 ± 3.7 to 8.9 ± 2.0 J in ibutilide-treated animals (p = 0.016); placebo administration produced no significant change in the ED_{50}.

In another study, the effects of ibutilide administered intravenously and in epicardial polyurethane monolithic controlled-release matrix dosage forms on DFT were evaluated in pentobarbital-anaesthetized open-chest dogs.[103] Ibutilide administered in a 20% by weight matrix formulation (n = 7), intended to provide the equivalent of 25 μg/kg administered intravenously, provoked a decrease in monophasic DFT from 7.23 ± 1.73 to 2.54 ± 0.56 J

(p = 0.38). However, intravenous ibutilide 25 μg/kg (n = 5) did not result in a significant reduction in DFT (from 7.62 ± 1.52 to 4.46 ± 1.21 J; p = 0.51). Administered in controlled-release matrices designed to deliver a lower ibutilide dose (3.5 μg/kg, n = 9), ibutilide was associated with a reduction in biphasic DFT from 3.42 ± 0.46 to 2.53 ± 0.34 J; p = 0.003. However, intravenous administration of ibutilide 2.5 μg/kg produced no significant change in biphasic DFT. The ibutilide doses studied in this investigation were substantially lower than those used in the study by Wesley et al.,[102] which explains the lack of efficacy of intravenous ibutilide in this study. Epicardial administration of low-dose ibutilide in controlled-release dosage forms resulted in significant reductions in DFT.

4.8.2 Clinical Studies

The effects of ibutilide on energy requirements for atrial defibrillation have been investigated. Oral et al.[104] randomized 100 patients with AF to transthoracic cardioversion alone or with pretreatment with ibutilide 1 mg infused over 10 minutes. The incidence of successful atrial defibrillation was significantly higher in patients who were pretreated with ibutilide (100% vs 72%; p < 0.001). In addition, transthoracic energy requirements for atrial defibrillation were significantly lower in patients who were pretreated with ibutilide compared with those who were not (166 ± 80 vs 228 ± 93 J; p < 0.001). In another study, the effects of ibutilide on facilitation of atrial defibrillation and atrial DFTs were determined using an internal defibrillation system in 24 patients with AF.[105] Defibrillating coils were introduced transvenously into the right atrium. Biphasic shocks were administered to all patients using a step-up protocol from 1 to 30 J. In patients in whom internal atrial defibrillation was provoked successfully, AF was re-induced. Ibutilide 1 mg was administered intravenously over a period of 10 minutes, after which internal atrial defibrillation was again performed. Internal atrial defibrillation was successful in 22 patients (92%) in the absence of pre-administration of ibutilide and in 23 patients (96%) following ibutilide pretreatment. The amount of energy required for atrial defibrillation was lower following ibutilide pretreatment compared with that in the absence of ibutilide pretreatment (8.28 ± 9.64 vs 13.89 ± 11.44 J; p = 0.0001).

4.8.3 Summary

Ibutilide decreases ventricular DFT in animals. Ibutilide facilitates and reduces energy requirements for atrial defibrillation in patients. (Level of evidence: B.)

4.9 Disopyramide

4.9.1 Animal Studies

Disopyramide did not significantly affect ventricular DFT compared with baseline values using an increment-decrement protocol in five anaesthetized dogs (4.4 ± 0.6 vs 4.2 ± 0.6 J).[79] In a subsequent study by the same investigators, disopyramide similarly had no significant effect on ventricular DFT compared with pretreatment values (4.4 ± 1.5 vs 4.4 ± 1.6 J) in eight anaesthetized dogs.[80]

4.9.2 Summary

Data from case reports and clinical studies are lacking. Available evidence from animal studies indicates that disopyramide has no significant effect on ventricular DFT.

4.10 Dofetilide

4.10.1 Animal Studies

The effect of dofetilide (an I_{Kr} channel inhibitor) on defibrillation energy requirements was compared with that of ambasilide (an inhibitor of both I_{Kr} and I_{Ks} channels) and placebo in an anaesthetized canine model of transvenous defibrillation.[35] Dofetilide significantly reduced biphasic defibrillation energy requirements by 21.9% ± 5.2% (p < 0.05 compared with placebo). Ambasilide also significantly reduced defibrillation energy requirements compared with placebo; there was no significant difference in the magnitude of reduction in defibrillation energy requirements between dofetilide or ambasilide.

In a placebo-controlled study that employed an open-chest canine model dofetilide was administered in escalating doses (low: 2.5 μg/kg bolus, 0.9 μg/kg/h; medium: 10 μg/kg bolus, 3.6 μg/kg/h;

high: 25 μg/kg bolus, 9 μg/kg/h).[106] Compared with that in the placebo group, DFT was significantly decreased in the dogs that received the highest dose of dofetilide. The effect of dofetilide on DFT was significantly correlated with dofetilide-induced changes in ventricular refractoriness and shock-induced refractory period extension.[106]

In a study designed to determine whether the effect of antiarrhythmic drugs on defibrillation efficacy is dependent on the defibrillation waveform, dofetilide was administered to seven dogs (loading dose of 20 μg/kg, followed by a continuous infusion of 0.2 μg/kg/min).[107] Dofetilide significantly reduced DFT regardless of whether the shocks were monophasic or biphasic.

4.10.2 Summary

Studies conducted in animals indicate that dofetilide reduces DFT. Data from human reports or studies are lacking.

4.11 Mexiletine

4.11.1 Animal Studies

Escalating doses of mexiletine resulted in elevation of DFT from 4.6 ± 1.2 to 6.1 ± 2.0 J ($p < 0.05$) in nine anaesthetized dogs; VF was not susceptible to defibrillation in three of the nine dogs studied.[80] In another study, mexiletine increased the mean DFT by 17% ± 16% in seven anaesthetized dogs.[107] Mexiletine was also reported to significantly increase ventricular DFT in anaesthetized dogs pretreated with flecainide.[91]

However, Sato et al.[108] reported conflicting results in a study conducted in ten anaesthetized dogs. Mexiletine was administered intravenously at a loading dose of 1, 2, 4, 6 or 8 mg/kg, followed by the same dose/kg/h. DFT was determined using an incremental protocol every 10 minutes, until 60 minutes after initiation of each maintenance dose. There was no relationship between plasma mexiletine concentration and DFT. A statistical comparison of DFT during each dose of mexiletine compared with pretreatment values was not provided, but the investigators concluded that mexiletine did not affect ventricular DFT.

4.11.2 Case Reports

Marinchak et al.[109] reported the case of a 64-year-old male patient who had undergone implantation of an ICD because of recurrent sustained VT that had resulted in cardiac arrest. Mexiletine therapy was initiated approximately 10 months after ICD implantation. Approximately 2 months later, during a magnet test, the ICD inappropriately discharged. During subsequent DFT testing, induced VF was refractory to shocks of 20 and 25 J, and an internal shock of 40 J was required for successful defibrillation. Mexiletine therapy was discontinued, because of concern that the drug may have elevated the DFT. Three weeks later, during replacement of the device's generator, induced VF was terminated with a shock of 20 J.

Crystal et al.[110] described the case of a 40-year-old male patient with idiopathic dilated cardiomyopathy and heart failure who underwent implantation of an ICD because of recurrent symptomatic nonsustained VT. During ICD implantation, DFT was determined to be 20 J. Approximately 9 months after ICD implantation, the patient experienced several episodes of VF, which were successfully defibrillated by the device. The patient was initiated on therapy with mexiletine (300 mg/day) and ventricular pacing was initiated for management of bradycardia. The patient was also receiving enalapril, furosemide, digoxin and carvedilol. Over the next few months, the frequency of ICD shocks declined, but symptoms of heart failure progressively worsened, which was presumed to be a result of ventricular pacing. At this time, the ICD was replaced with a dual-chamber, rate-responsive ICD, which delivers biphasic shocks. After connection of the new ICD, DFT testing was performed, during which induced VF could not be defibrillated with the device, including failure of two rescue shocks. Mexiletine was discontinued and DFT testing was repeated 4 days later. Successful defibrillation was achieved with two consecutive shocks of 23 J. A subsequent 20-J shock was ineffective, but a rescue shock of 31 J was effective. In addition, a subsequent episode of spontaneous VF was successfully terminated by the device.

4.11.3 Clinical Studies

In a prospective, observational study in 22 patients with early-generation ICDs, DFT was evaluated at the time of ICD implantation and generator replacement (mean follow-up 24 ± 6 months).[63] Mean DFT increased from 14.1 ± 3.0 to 20.9 ± 5.4 J ($p < 0.001$) in patients receiving amiodarone 400 mg/day. There was no significant change in DFT in patients receiving therapy with mexiletine 720 mg/day.

4.11.4 Summary

Although not supported by one clinical study, animal data and a small number of case reports suggest that mexiletine may increase the DFT. (Level of evidence: C.)

4.12 Moracizine

4.12.1 Animal Studies

The effect of moracizine on ventricular DFT was studied in 18 pentobarbital-anaesthetized pigs.[90] Moracizine (administered as a 2-mg/kg intravenous loading dose followed by a continuous infusion of 1.5 mg/kg/h) increased DFT by 14% from baseline (12.1 ± 2.8 vs 13.8 ± 5.2 J; $p = 0.03$ compared with the effects of placebo). However, the combination of moracizine and lidocaine increased DFT by 84%, compared with a 27% increase associated with lidocaine alone. In a study of 11 pentobarbital-anaesthetized dogs,[111] moracizine 2 mg/kg administered intravenously increased ventricular DFT from a baseline value of 7.5 ± 4 to 9.4 ± 4 J ($p = 0.006$). Pharand et al.[47] randomized 13 pigs to receive long-term therapy with oral moracizine 10–15 mg/kg three times daily or placebo. Baseline ventricular DFT measurements were performed prior to randomization and on the morning of the 4th day of oral therapy. Moracizine did not significantly alter DFT compared with placebo.

4.12.2 Case Reports

Tworek et al.[112] reported the case of a 64-year-old man who underwent ICD implantation following an episode of SCD. At the time of ICD implantation the DFT was 15 J. The ICD was replaced 3 years later, at which time the DFT was 16 J. Therapy with moracizine was initiated 7 months later for the management of VT; 3 days later, during an electrophysiological study, the DFT was measured at 28 J. The patient subsequently died as a result of intractable VT.

4.12.3 Summary

Acute therapy with intravenous moracizine increases ventricular DFT in anaesthetized dogs or pigs. Long-term therapy with oral moracizine exerted no effect on ventricular DFT in anaesthetized pigs. Clinical data regarding the effects of moracizine on ventricular DFT are relatively lacking, although one case report suggests that the drug may increase DFT. (Level of evidence: C.)

4.13 β-Blockers

4.13.1 Animal Studies

Data regarding the effects of β-blockers on DFT are conflicting. Intravenous propranolol 0.2 mg/kg resulted in no significant influence on DFT in anaesthetized dogs ($n = 6$) or pigs ($n = 6$).[98] In addition, intravenous atenolol 3.0–6.0 mg/kg exerted no significant influence on ventricular DFT in anaesthetized pigs ($n = 8$).[43] In a study of 11 conscious dogs, propranolol increased ventricular DFT from 10.6 ± 3.0 to 14.6 ± 3.9 J ($p = 0.02$) and reversed the effects of isoprenaline, which significantly decreased DFT.[113]

4.13.2 Case Reports

Melichercik et al.[114] reported the case of a 69-year-old male with coronary artery disease, a past myocardial infarction, and LVEF of 30% who underwent implantation of an ICD as a result of spontaneous and inducible sustained VT. Following ICD placement, the DFT was 14 J. During the hospital admission during which the ICD was implanted, therapy with carvedilol 12.5 mg/day was initiated for the management of NYHA class III heart failure. The carvedilol dose was increased to 25 mg/day on the 7th day of hospitalization and the dose was further increased to 25 mg twice daily on the next day (a rapid dose escalation). Seven days after ICD implantation, prior to discharge, the DFT was measured again and found to be >30 J and the induced

VF required termination via external defibrillation. Carvedilol therapy was discontinued; 14 days later, the DFT was 17 J. It is unclear whether the increased DFT occurred as a direct pharmacological effect of the drug, or whether the rapid escalation of the carvedilol dose may have caused volume overload, which has been reported to increase DFT.[50]

4.13.3 Clinical Studies

In the substudy of the OPTIC trial, β-blockers decreased DFT from 8.77 ± 5.15 to 7.13 ± 3.43 J ($p = 0.03$).[2] In contrast, there was a nonsignificant increase in DFT in patients receiving therapy with β-blockers and amiodarone, and the change in mean DFT in the β-blocker group compared with that in the combined amiodarone plus β-blocker group was significantly different ($p = 0.006$).

4.13.4 Summary

Available clinical data suggest that β-blockers do not increase ventricular DFT and may reduce it. (Level of evidence: B.)

4.14 Verapamil

4.14.1 Animal Studies

The effects of verapamil on ventricular DFT were studied in 36 open-chest anaesthetized pigs, and compared with that of placebo in eight pigs.[115] The animals were randomized to one of four doses of intravenous verapamil. At the highest administered dose (0.51 mg/kg, adjusted for metabolic bodyweight [to the 0.75 power]), verapamil was associated with a significant increase in DFT (from 6.3 ± 0.6 to 8.2 ± 1.1 J; $p < 0.05$). At the lower doses tested, verapamil (or placebo) was not associated with significant changes in ventricular DFT.

4.14.2 Clinical Studies

Jones et al.[97] investigated the effects of oral verapamil on ventricular epicardial DFT in 12 patients undergoing surgery for arrhythmias. Verapamil significantly increased DFT (from 3.9 ± 2.2 to 6.5 ± 2.9 J) in this setting.

4.14.3 Summary

Minimal data exist regarding the effect of verapamil on DFT. One study in humans suggests that verapamil increases DFT; the clinical significance of this change in DFT is unclear. (Level of evidence: C.)

4.15 Digoxin

4.15.1 Animal Studies

In a study of closed-chest anaesthetized dogs (n = 6) and pigs (n = 6), intravenous digoxin (0.4 mg/kg) exerted no significant effect on ventricular DFT.[88]

4.15.2 Summary

There is no evidence to suggest that digoxin influences ventricular DFT.

4.16 Venlafaxine

4.16.1 Case Reports

Carnes et al.[116] reported the case of a 35-year-old woman in whom an ICD was implanted as a result of nonischaemic cardiomyopathy and a history of sudden cardiac arrest. The patient also had a history of depression, for which she was receiving therapy with venlafaxine 75 mg three times daily, and bupropion 200 mg/day in the morning and 100 mg/day in the evening. Following ICD implantation, the device failed to achieve defibrillation with shocks of 5 and 20 J during initial testing, and seven external shocks were required before defibrillation was achieved. Venlafaxine therapy was then tapered and discontinued over a period of 4–5 days, and bupropion therapy was tapered and discontinued over a period of 48 hours. Four days after discontinuation of antidepressant therapy, the ICD was tested again. During the first three tests, defibrillation was achieved with shocks of 25–28 J, and in the other two tests, defibrillation occurred with shocks of 35 J. Based on data indicating that the drug is an inhibitor of cardiac sodium channels, the authors attributed the elevated DFT to venlafaxine. Plasma venlafaxine concentrations were determined and found to be within the therapeutic range.

4.16.2 Summary

Data from a single case report suggests that venlafaxine may increase DFT. (Level of evidence: C).

4.17 Anaesthetic Agents

4.17.1 Case Reports

Cohen et al.[117] reported the case of a 26-year-old man with dilated cardiomyopathy and frequent episodes of VT. Prior to ICD implantation, he was treated with mexiletine and propafenone. The patient underwent ICD placement and 1 day later DFT testing was performed. Following intravenous propofol 320 mg, DFT was >31 J, and an external shock of 360 J was required for defibrillation. Twenty minutes later, conscious sedation was performed with midazolam, during which DFT was recorded as 21 J.

4.17.2 Clinical Studies

Weinbroum et al.[118] randomized 80 patients undergoing ICD implantation in blinded fashion to anaesthetic regimens including halothane, isoflurane, fentanyl or lidocaine combined with propofol. Anaesthetic regimens including halothane, isoflurane or fentanyl each increased the ventricular DFT during peri-implantation DFT testing. The combination of lidocaine and propofol had no significant effect on ventricular DFT.

In contrast, anaesthesia regimens of inhaled isoflurane or intravenous propofol had no significant effect on ventricular DFT in 68 patients who underwent ICD implantation.[119]

4.17.3 Summary

Data regarding the influence of anaesthesia on ventricular DFT are conflicting. In patients undergoing DFT testing following ICD implantation, anaesthesia may be considered as an cause of unexplained elevated DFT values. (Level of evidence: C.)

5. Summary and Conclusions

While the ICD is clearly superior to drug therapy in preventing death from ventricular arrhythmias in patients who have an increased risk of sudden death, a large proportion of patients who have ICDs nonetheless are concomitantly taking antiarrhythmic drugs and other medications for adjunctive cardiac rhythm management as well as other indications. Many of these agents have an effect on the defibrillation capacity. Specific cardiovascular drugs, including amiodarone, lidocaine, mexiletine, moracizine, carvedilol and verapamil, have been associated in studies and/or case reports with elevations in ventricular DFT. In contrast, drugs such as sotalol and β-blockers may decrease ventricular DFT and facilitate defibrillation. Other drugs, including venlafaxine and anaesthetic agents, may increase DFT. These effects must be considered when managing patients who have an ICD and may need additional drug therapy.

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