Management of high defibrillation threshold

Eric R Uyguanco, Aaron Berger, Adam S Budzikowski, Moshe Gunsburg and John Kassotis

The implantable cardioverter defibrillator (ICD) has become the primary therapy for the treatment of potentially lethal ventricular arrhythmias. Ventricular arrhythmias encompass a spectrum of rhythm disturbances ranging from the occasional monomorphic ventricular premature complex to the almost universally fatal ventricular fibrillation. Our understanding of the mechanisms of ventricular fibrillation and defibrillation is still in evolution. At present, the most common ICD configuration consists of a pectoral pulse generator (active-can) with a bipolar transvenous dual coil lead. A transvenous system with an active-can has improved defibrillation thresholds and the ease of implantation. However, there are various clinical scenarios in which patients with high defibrillation threshold (DFT) are encountered. Although the incidence of high DFT patients is low, it is of significant concern since it may account for sudden cardiac death in patients with ICDs. At present, there are few clinical trials that are rigorous and well designed, and which can define a perfect methodology for the treatment of high DFT patients. In this review, in the context of commonly encountered clinical scenarios, we discuss therapeutic strategies to help manage patients with high DFT.

Keywords: biphasic shock • defibrillation threshold • implantable cardioverter defibrillator • shock impedance • sudden cardiac death • tilt • ventricular fibrillation

With rapidly expanding indications for implantable cardioverter defibrillator (ICD) insertion, the ICD has evolved as an important medical device for the primary prevention of sudden cardiac death. The prevalence of sudden cardiac death in the USA is estimated to be 400,000–500,000 patients annually. This is the leading cause of mortality in the USA today.

With the ease of ICD implantation, the major task remains proper patient selection and identification. Defibrillation threshold (DFT) testing has been considered an important part of the ICD insertion. Recent publications appear to argue the imperative need for DFT testing during implantation, quoting a high effectiveness for the current generation of defibrillators and a nontrivial rate of associated complications [1–3]. On the other hand, a small percentage (11–14%) will have high DFT during implantation [3,4]. Traditionally, a high DFT is defined as a DFT value that is less than 10 J lower than the maximum output of the generator. For the purposes of this discussion, this will serve as the definition of a high DFT despite recent published literature suggesting that either the lack of achieving a 100% safety margin or a DFT value greater than 15 J defines a high DFT [4,5].

Although patients with a high DFT pose a challenge, long-term mortality does not seem to be affected, even when less than the 10 J safety margin is achieved [4–7]. The most troubling patients are those who cannot be defibrillated at all. System modifications can provide adequate safety margins in the majority of these patients. Although a universal solution does not exist, this review will attempt to give the reader the background to understand the basic principles of ventricular fibrillation (VF) and defibrillation and to propose a rationale for the therapeutic strategy to help manage patients with high DFTs. The following clinical scenarios commonly encountered in clinical practice will serve as the focal point of this discussion:

• A middle-aged man with a past medical history remarkable for a dilated nonischemic cardiomyopathy recently resuscitated by emergency medical services in the field for an episode of VF is presented for the implantation of an ICD. The patient had a left ventricular ejection fraction of 20%. During intraoperative testing, VF was only converted to sinus rhythm with a 35-J shock, failing to achieve a 10-J safety margin;
An elderly woman, whose past medical history is significant for an ischemic dilated cardiomyopathy (ejection fraction: 35%), underwent the implantation of an ICD for primary prevention. Her DFT at the time of insertion 2 years ago was 20 J. She received a device capable of delivering 35 J. She experienced a prolonged episode of syncope requiring intubation in the field. The patient arrived at the Emergency Department intubated, hemodynamically stable and was later admitted to the Critical Care Unit. Device interrogation revealed an episode of VF, which failed to defibrillate at 35 J twice. The patient is unresponsive. There was no recent change in medication since implantation; however, the patient’s most recent echo from her private medical physician revealed an ejection fraction of 15–20%.

A young man, with a history of Brugada syndrome and an aborted episode of sudden cardiac death underwent the insertion of an ICD 3 years ago. The patient recently experienced erectile dysfunction and had started taking sildenafil. The patient’s DFT at implantation was 18 J. He received a device capable of 30 J delivery. He experienced an episode of ventricular tachycardia, and the ICD restored sinus rhythm after a 30 J shock, failing at 20 and 24 J.

Electrical determinants of the defibrillation threshold

Pathogenesis of ventricular fibrillation

Ventricular fibrillation is an abnormal rhythm disturbance characterized by a very rapid uncoordinated propagation of electrical wavefronts, creating a fluttering contraction of the ventricles of the heart. VF disrupts the synchrony between the heartbeat and the pulse beat, leading to hemodynamic instability with an almost universally fatal outcome. VF is most commonly associated with myocardial infarction, although there is an idiopathic form of the syndrome. The mainstay of treatment is rapid cardic defibrillation.

Theory of ventricular defibrillation

Defibrillation requires the administration of energy (electric shock), in the form of voltage designed to create a sufficient gradient across the fibrillating myocardium to extinguish the propagating fibrillatory wavefronts. In addition, the voltage gradient must prevent the initiation of new wavefronts capable of re-establishing VF.

A complex interplay of several variables ensures the success of defibrillation. The factors important in determining the success of defibrillation involve the characteristics of the defibrillation (or delivery) system and the substrate (state of the myocardial tissue).

Concept of the defibrillation threshold

The DFT has been traditionally used to describe the delivered energy, characterizing a given defibrillation system, which reproducibly terminates the fibrillatory state and restores sinus rhythm. The word ‘threshold’ implies the titration of delivered energy until one reaches a level where reproducible defibrillation fails. This is not clinically practical, and the energy required to reproducibly terminate the fibrillatory state is usually reported as the DFT.

One is actually reporting the lowest energy of defibrillation. This energy must be sufficient to stimulate the fibrillating tissue, restoring sinus rhythm, which is administered by either an external or an internal shocking system. This discussion will focus on implantable shocking systems.

Various techniques used to establish the defibrillation threshold

Several methods for DFT testing have been established and will be briefly described here. All testing algorithms require appropriate recovery time between inductions, usually 5 min. One method of testing is the single energy success technique, where VF is induced and the first shock is programmed to provide a 10-J safety margin. This can be repeated twice or even three times. Although this method may not necessarily establish the true DFT, it is practical and avoids multiple VF inductions, which can be associated with deleterious hemodynamic consequences and myocardial shock injury. This makes it necessary to titrate to the lowest energy of defibrillation.

Another technique is a step-down method. Serial VF induction is performed with a graded initial delivered energy response until failure is established. The lowest energy that successfully defibrillates the myocardium establishes the DFT. This is repeated once or twice to ensure success.

The binary search technique is a method where a random energy is delivered to terminateVF depending on success or failure. A lower or higher energy level is used, again in a step-wise fashion to establish the DFT.

A permutation of the aforementioned technique is the Bayesian search method, developed by St Jude Medical. With this technique, four shocks are delivered to establish the DFT.

With the upper limit of vulnerability testing technique, synchronized T-wave shocks are delivered, each with decreasing energy. The lowest energy shock that fails to induce VF is the upper limit of vulnerability. There is a strong correlation between the upper limit of vulnerability and DFT. Therefore, this method may have an advantage over true DFT testing, by allowing fewer episodes of VF to be induced.

Basic physics of shock strength

The shock energy (in joules), which is a function of voltage, current and pulse duration, is a determinant of shock strength (Box 1).

Most recently, the predictive value of this variable has come into question. Investigators have proposed alternative parameters, such as the late peak voltage, peak current or average current as more reliable quantifiers of successful defibrillation.

Box 1. Shock energy calculations.

- Energy (E) = voltage (V) × current (I) × duration (s)
- Shock energy (E) joules = (V² × time)/impedance (Ohms)
- Sample calculation:
  Energy delivered to the heart by an ICD that has a shock lead impedance of 30 Ohms delivering 9 V for 20 s:
  Shock energy (joules) = [(9)² × 20]/30 = 54 joules

ICD: Implantable-cardioverter defibrillator.
For a given delivered energy, the voltage gradient created across the fibrillating myocardium is a function of voltage, current and the characteristics of the pulse delivered. An adjustable variable, which can alter the characteristics of pulse width, is the tilt. Increasing energy may not necessarily increase the success of defibrillation. For example, one can increase the duration of a pulse without improving the ability to defibrillate the myocardium. In fact, unduly prolonging pulse duration may decrease the efficacy of defibrillation. As the pulse duration of the shock increases, the degree of tilt increases.

Evolution of the biphasic waveform, the concept of tilt and other adjustable variables: application to clinical practice

The advent of the biphasic waveform has greatly influenced defibrillation by improving efficacy. Figure 1 illustrates a typical biphasic waveform with tilt. The biphasic waveform serves a dual role in defibrillation. The first component extinguishes as many of the established propagating fibrillatory waveforms as possible, while the second component (phase 2) removes the residual membrane charge and counters the ill effects of the first discharge by preventing the creation of new wavefronts capable of re-initiating VF. This so-called ‘burping theory’ has led some ICD manufacturers to change the programming characteristics of tilt by modifying the software to allow more flexibility in programming the duration of each component of the biphasic pulse signal [10].

Adjustable parameter for the optimization of defibrillation threshold

Variables that influence tilt include the shock impedance and the membrane time constant of a given patient. These reflect the characteristics of the myocardial substrate, which is unique to a given patient. In clinical practice, the shock impedance is a measurable parameter. The higher the impedance, the longer it takes a given shock to achieve its maximal value. Therefore, the ideal shock duration will increase as the impedance increases. In a fixed tilt defibrillation system, the shock duration does not change with changing impedance. In addition, fixed tilt systems do not afford the flexibility of adjusting pulse width to change tilt to adapt to changing shock impedance. This may explain changes in the DFT with time.

Multiple studies in humans have confirmed that the ability to change the pulse duration of the shock will improve the ability to defibrillate [11]. Several investigators have shown that defibrillation improves with optimization of the shock waveform compared with a fixed tilt system [12].

Conflicting evidence exists as to whether a single versus dual coil transvenous system optimizes DFT values [13]. Several manufacturers offer, or are in the process of offering, a programmable superior vena cava (SVC) on/off feature for DFT management, which affords greater programming flexibility (see the ‘Acute management of the patient with high DFTs’ section). By contrast, pectoral systems can employ the ICD generator ‘hot-can’ as a second electrode in concert with the proximal coil or alone in an attempt to lower DFTs. Data have confirmed that rightsided implants have higher DFTs than the traditional left-sided implants [9].

Last, one has to have an understanding of shocking polarity. Most data suggest that anodal defibrillation (i.e., first phase has the right ventricular shocking electrode as positive with the ICD-can and/or the proximal electrode negative) requires less energy to defibrillate the heart than cathodal defibrillation [13].

In summary, our current understanding of VF is rapidly expanding. Our progress in better understanding defibrillation mechanisms is pivotal, as the ICDs are at the forefront of the treatment of sudden cardiac death. With our present knowledge, optimizing the defibrillating system requires a thorough understanding of all programmable parameters and the interplay of the defibrillating system and the myocardial substrate.

Acute management of the patient with high DFT

The first vignette is a scenario commonly encountered in clinical practice. There are several maneuvers available to the implanting physician to optimize the DFT. This is often a function of the myocardial substrate and it is in the hands of the implanter to modify the various components of the defibrillation system to optimize thresholds.

Rule out pneumothorax

A commonly-missed cause of high DFTs or DFT failure is pneumothorax, which is a known complication of prepectoral device insertion. It is our recommendation that when DFT failure occurs or when DFTs are high, a thorough fluoroscopic evaluation should be performed intraoperatively. Higher defibrillation impedance may be an early indicator of the presence of a pneumothorax [14]. It has been reported in the literature that resolution of pneumothorax has resulted in an improved shock impedance and DFT [14,15].
Lead position & vector programming
The goal of a defibrillation system is to create a vector of defibrillation that encases as much of the potentially fibrillating myocardial tissue as possible. First, the implanter should assess the position of the distal coil of the defibrillation lead. The distal coil of the lead should clear the tricuspid annulus and assume a position well into the right ventricle, ensuring that the lead does not straddle the tricuspid valve. This will allow the defibrillation waveform to envelope a larger portion of the left ventricle, simultaneously avoiding iatrogenic tricuspid regurgitation.

While adjusting the distal tip, one must pay attention to the resultant position of the proximal coil. The ideal location of the proximal (SVC) coil is a location at the SVC–right atrial (RA) junction. The location of the proximal coil will influence the direction of the defibrillation waveform. A location that is too far into the atrium or too high in the subclavian may cause dissipation of energy and reduce the resultant voltage gradient across the fibrillating substrate.

Figures 2A & B are chest x-rays illustrating the location of the proximal and distal coils in a left- and right-sided implantation, respectively.

Adjusting the slack on the lead is a useful technique, which can adjust and optimize the location of the proximal coil and its distance from the distal tip. Therefore, one has to assess the patient’s body habitus and heart size (dilated or small) in order to select a lead with the appropriate length. This maneuver is not always reliable preoperatively and the implanter should be aware that they have the option of changing lead length. In addition, a transvenous lead with different spacing between the proximal and distal coil is useful for select patients but the utility of this may be limited [16].

It has been thought that an apical position of the distal coil would significantly reduce the DFT. Recently it has been demonstrated that the DFT is minimally lower in an apical as opposed to high septal RV position [17,18].

Nevertheless, if one encounters the high DFT patient intraoperatively, one should reserve the option of repositioning the lead to a more apical location in an attempt to lower DFT.

In addition, one can move the defibrillator generator to a medial position to optimize the defibrillation axis. If available, one can reprogram the tilt according to defibrillation impedance measurement by optimizing the pulse duration of the initial phase of the defibrillation waveform. The initial pulse duration should be programmed to 4 ms [11]. More detailed algorithms are available from the device manufacturer [14]. Often these simple measures result in acceptable DFT.

It is our practice to place the lead in the apical septum of the right ventricle and program anodal defibrillation shock polarity before DFT testing (anecdotal experience > 1000 patients [KASSOTIS ET AL., UNPUBLISHED DATA]). The next step when encountering the high DFT patient is to disconnect the proximal coil from the defibrillation system. Should these measures fail, and if the use of a higher energy device has already been attempted (offered by most manufacturers), the next step is placement of a subcutaneous array.

Addition of a subcutaneous array
Placement of a subcutaneous array/coil lowers the DFT. Mechanisms thought to contribute to the reduction in DFT include shortening the first phase of the biphasic impulse (see ‘Electrical determinants of DFT’ section). In addition, the array/coil serves to further encase the myocardial tissue within the defibrillation axis. Therefore, the addition of an array/coil improves the efficacy of defibrillation by capturing more of the propagating fibrillatory waves during the first phase and preventing the initiation of new wavefronts, which can potentially reinitiate VF.

We recommend implantation of the subcutaneous coil via a separate incision in the midaxillary line. This location makes the insertion easier by correcting the curvature of the chest. It is our preference to use a single subcutaneous coil rather than array due to the ease of placement. The coil should be under fluoroscopic guidance in advance so that the lead tip is just over the spine (Figure 2C). Caution must be exercised, avoiding insertion of the coil into the pleural cavity. One should suspect pleural involvement if the patient experiences prolonged postoperative pain. In most cases, even if the subcutaneous coil has entered the pleural space, these patients do not require a lead extraction (anecdotal experience).

With refinements in ICD technology, abdominal implants have dramatically dropped over the last decade. However, there are circumstances where an abdominal implant is required (e.g., need for radiation therapy, whose window is encroaching on the generator).

---

**Figure 2.** Chest x-rays illustrating the proper insertion of an implantable-cardioverter defibrillator. (A) Left-sided implantation. (B) Right-sided implantation. (C) Placement of a subcutaneous array.
For patients with abdominal implants, it is important to ensure that the defibrillator generator is inactive (cold-can), which can be achieved either with electronic reprogramming or by ordering a special generator from the manufacturer. Often these patients have existing epicardial lead systems. In a high-DFT patient, with no improvement in the safety margin with a change in waveform polarity, a new transvenous lead system should be implanted.

Anecdotally, DFTs tend to be higher in patients who undergo a right-sided compared with a left-sided ICD implantation. Although there are no controlled human studies, this has been shown in animal models [19]. It is our practice to use a single coil defibrillator lead in these patients. If the usual measures described fail to improve the DFT, assuming that left-sided venous access is unavailable, we recommend extending the lead to the left, and the generator placement should be in a left subpectoral position.

Figure 3 summarizes the management of the patient with acutely elevated DFTs. There are several programmable features of the newer generation ICD and lead configuration, which make the need for an array infrequent.

**Changes in defibrillation threshold with time**

The stability of an ICD’s energy requirements over time was first evaluated in defibrillating lead systems consisting of a transvenous spring electrode either coupled with an apical, left lateral ventricular patch electrode, or coupled to two ventricular patch electrodes. Such lead systems required implantation via a subxiphoid, median sternotomy, or with a left anterior thoracotomy approach. The first large long-term clinical follow-up study demonstrated the temporal stability of the DFT in patients with the ICD and a patch–patch lead system [20]. Patients with a transvenous spring electrode–patch lead configuration experienced an upward trend in the defibrillation energy requirements over time.

Several studies have reported a late increase in DFT with transvenous and other hybrid lead configurations [21–29]. Over the years, ICDs have undergone a major evolution. The most common configuration consists of a pectoral pulse generator (active-can) with a bipolar transvenous dual coil (proximal SVC and distal) lead. This configuration requires less technical skill to implant surgically and provides defibrillation at energy levels comparable to those reported with epicardial lead systems [30–32]. The evolution to a transvenous lead system has reduced perioperative morbidity, mortality, hospital length of stay and cost compared with the traditional epicardial approach [33–35].

**Factors that influence temporal changes**

Several factors influence the stability of the DFT over time. The most important factors include the specific lead system utilized and the defibrillation waveform. Epicardial lead systems have a stable DFT over time [36,37]. On the contrary, an increase in DFT has been reproducibly reported with use of monophasic defibrillation waveforms in nonthoracotomy lead systems [21–24]. The use of biphasic defibrillation waveforms prevents the chronic increase in DFT observed with monophasic waveforms in a dual-coil transvenous lead system [38]. In another study, 15% of patients with a biphasic nonthoracotomy lead system experienced a 10 J and over increase in the DFT requiring reprogramming of the device. Up to 3% of patients required revision of the defibrillation system [27]. With a biphasic waveform in a hybrid lead system that integrates transvenous and subcutaneous components long-term increases in DFT are also observed [28,29].

Long-term follow-up of temporal changes in DFT specifically with a biphasic dual-coil, active pectoral lead system, demonstrated that the DFT declines significantly during the first 2 years after implantation with no clinically significant increases [39]. The larger multicenter Low Energy Safety Study supported these findings. DFTs were followed for 2 years after implantation [40]. The stability of the DFT beyond 2 years remains unclear.

**Mechanisms of temporal change**

The mechanisms responsible for the temporal change in DFT remain unclear. An increase in shock impedance over time is sufficient to account for the increase in DFT in a monophasic transvenous lead system [41,42]. However, biphasic DFTs were unchanged despite a significant increase in the shock impedance [38]. This suggests that shock impedance is an important determinant of DFT energy for monophasic, but not biphasic, waveforms [38].

In the previous study, the long-term biphasic DFT declined significantly with a dual-coil, active pectoral lead system [39]. The authors of this study concluded that this decrease in DFT is independent of the waveform or changes associated with maturation of the transvenous lead. The chronic DFT, confirmed in another study, did not change with this particular waveform configuration, lead and an inactive pectoral pulse generator [38]. The authors also maintain that the stress of surgery was unlikely to account for the higher DFT at implantation because there was no significant difference between the DFT values at implantation and before discharge. However, because the pulse generator is a component...
of the defibrillation system, the temporal decline in DFT may be related to maturation of the pocket [39]. With the dual-coil, active pectoral pulse generator configuration, current can flow from the distal right ventricular coil to either the proximal coil or the pulse generator. Maturation of the pulse generator pocket may result in a favorable change in the distribution of current between these two pathways, thus improving defibrillation efficacy.

On the contrary, maturation of the lead system can contribute to the upward DFT shift sufficiently to erode or erase the defibrillation safety margin over time [43]. Changes occur over time between the electrodes and surrounding tissue that can contribute to increased energy requirements [22–24]. In addition, changes in myocardial substrate over time, possibly due to disease progression, may significantly contribute to the upward DFT shift. Changes in substrate include worsening congestive heart failure, dilatation or hypertrophy of the left ventricle, increase in severity of left ventricular dysfunction and new myocardial infarction. This may play a major role in the upward drift of the DFT and it behooves the clinician to be aware of the possibility, especially when there has been a major change in the myocardial substrate.

Management of high DFT owing to temporal changes
Several options are available and have been developed over time to manage patients with high DFT, as illustrated in the second clinical vignette. This patient experienced a high DFT as a result of a change in myocardial substrate due to worsening of the left ventricular systolic function. These patients should undergo an ischemic evaluation given the possibility of disease progression. Revascularization of ischemic or hibernating myocardium may reduce DFT. Aggressive pharmacologic treatment may improve systolic function, potentially improving DFT. The patient should have repeat DFT, ensuring an acceptable safety margin. Should the DFT remain high, additional maneuvers are required. We recommend starting with the least invasive and costly option. Simply reprogramming the RV coil polarity to positive (anodal) can significantly improve the DFT and should be the first step. The use of the RV coil as the cathode is usually the nominal setting in most devices (Table 1). With monophasic waveforms, anodal defibrillation results in a lower DFT when compared with cathodal defibrillation [44,45]. This also applies to biphase waveforms; however, the reduction in DFTs was less dramatic [46–50]. If changing the RV polarity is ineffective, one can adjust the tilt. Several studies have illustrated a reduction in DFT by altering the duration of the first and second phase of the biphase waveform compared with a fixed duration [51–54]. Currently only one manufacturer offers a device with the programming capability to adjust the duration of the phases of the waveform (Table 1).

Reprogramming the configuration to remove the SVC coil from the circuit, if available, can reduce the DFT, especially with low lead impedance, in effect creating a unipolar configuration. This configuration results in a lower DFT with an increase in current [55,56] associated with a higher DFT tissue gradient, implying a less efficient distribution of voltage gradient.

If the noninvasive maneuvers fail to improve the DFT, several invasive options are available. Simply switching to a high energy device may offer an adequate safety margin and avoid additional surgery. The addition of a right atrial/SVC lead may improve the DFT by decreasing the shock impedance, increasing the current of the shock delivered through the RV coil, and reducing the pulse width [56,57]. An SVC lead can be inserted in the left innominate or azygos vein [58–60]. Alternatively, the addition of a coronary sinus lead may improve DFT [61]. As mentioned previously, one can insert a subcutaneous array/coil.

In the event that an adequate safety margin is still not achieved, these patients may still benefit from the insertion of a high-energy device if defibrillation is achieved with a lower safety margin or the highest output delivered by the device [62]. One can attempt to lower the DFT by the addition of an epicardial or pericardial patch. As a last resort, empiric medical therapy using antiarrhythmic agents known to lower DFT, such as dofetilide or sotalol, may be attempted. It should be mentioned that it is our current practice and recommendation that a 100% safety margin should be achieved when possible, as opposed to the traditional 10 J safety margin.

**Figure 4** provides an algorithm summarizing the various approaches to managing the patient with high DFT.

### Effect of medications on defibrillation threshold

Our third vignette highlights another common scenario encountered with increased frequency clinically, namely, a change in DFT after the introduction of a new medication (sildenafil).

Following the implantation of an ICD, many patients will have their medication changed. Drug therapy present at the time of implantation may be withdrawn, or new medications added, which may negatively impact the DFT. Drugs can either

<table>
<thead>
<tr>
<th>Device reprogramming</th>
<th>RV coil polarity (default)</th>
<th>Programmable tilt (optimize phase duration)</th>
<th>Programmable removal of SVC coil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Scientific (Guidant)</td>
<td>Cathodal (negative)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Medtronic</td>
<td>Anodal (positive)*</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>St Jude Medical</td>
<td>Anodal (positive)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*In older generation devices RV coil polarity was cathodal (negative).

*Only the newest generation of devices.

RV: Right ventricular; SVC: Superior vena cava.
lower or raise the DFT, therefore obtaining a comprehensive drug history is imperative in the management of a patient who has experienced a change. As previously mentioned, medications can be used to optimize DFTs when all other options have been exhausted.

Antiarrhythmic agents often alter the DFT, most commonly observed with sotalol and amiodarone. In particular, amiodarone use is common when patients experience frequent ICD discharges.

In general, sodium channel blockers and calcium channel blockers will raise the DFT, whereas potassium channel blockers will raise the DFT, whereas potassium channel blockers will raise the DFT. Initial reports suggested that intravenous amiodarone action, has contributed to conflicting reports regarding its effect on DFT. The remainder of this discussion will focus on several of the more common medications used in clinical practice known to alter DFT. A more comprehensive discussion is beyond the scope of this review.

**Amiodarone**

Amiodarone is classified as a class III (potassium channel blocker) agent; however, it also exhibits β-blocker, sodium channel and calcium channel-blocker properties. As a potassium channel blocker, amiodarone acts to slow conduction while prolonging refractoriness. In addition, it prolongs the QRS duration (class I sodium channel blocker effect), as well as displaying nonspecific adrenergic blocking properties (class II) and dromotropic suppression (class IV effect) [60].

The difference in the electrophysiological properties of intravenous and oral amiodarone, as well as its various mechanisms of action, has contributed to conflicting reports regarding its effect on DFT. Initial reports suggested that intravenous amiodarone reduced DFT [65], while chronic oral amiodarone treatment increased the DFT [66].

These findings compelled the Heart Rhythm Society to recommend reassessment of DFT after initiation of antiarrhythmic drug therapy [67]. At the time of this recommendation, there were no prospective clinical trials testing this hypothesis.

The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial was the first randomized clinical trial to evaluate the effects of amiodarone and sotalol on DFT [67]. Patients were randomized to a β-blocker, amiodarone and β-blocker, or sotalol arm. After the baseline DFT was measured, the DFT was reassessed approximately 60 days after the initiation of therapy. With the exception of one outlier, the DFT did not exhibit a significant change. The authors concluded that this study does not support the practice of DFT reassessment after the institution of chronic amiodarone therapy.

**Sotalol**

Although sotalol is a class III antiarrhythmic agent, at lower doses, it exhibits antiadrenergic activity. The class III effect includes slowing of sinus node activity, increased atrial–ventricular nodal refractoriness and a decreasing atrial–ventricular nodal conduction. Sotalol exerts its class III effect by prolonging the monophasic action potential of both atrial and ventricular tissue resulting in a prolongation of the respective effective refractory periods. With a prolongation of ventricular refractoriness, sotalol should lower the DFT. In fact, early studies demonstrated that intravenous β-sotalol lowered DFTs by an average of 32% [68]. Most recently, the OPTIC trial revealed no significant decrease in the DFT with sotalol therapy [68].

**Mexiletine**

Mexiletine is a class IB antiarrhythmic agent, considered the oral equivalent of lidocaine. Mexiletine is used in patients with ventricular arrhythmias who have responded to lidocaine. Mexiletine can serve as adjunctive therapy with amiodarone in patients with difficult ventricular arrhythmias. Mexiletine as a class I agent would be expected to increase the DFT. There are no prospective clinical trials assessing the effect of mexiletine on DFT; however, several case reports have implicated this agent as a potential cause of an elevated DFT [69,70].

**Dofetilide**

Dofetilide is a class III antiarrhythmic agent. Dofetilide has been reported to decrease the DFT in patients undergoing ICD implantation [71].

---

**Figure 4. Algorithm for management of high defibrillation threshold with time.**

DFT: Defibrillation threshold; SVC: Superior vena cava.

---

Amiodarone and sotalol lowered DFTs by an average of 32% [68]. Most recently, the OPTIC trial revealed no significant decrease in the DFT with sotalol therapy [68].
β-blockers
Propranolol and carvedilol have been tested with regard to their effects on DFT [72,73]. Propranolol showed no significant effect on DFT, while carvedilol could prevent the deleterious effect of catecholamines on DFT. In addition, the authors feel that the positive effects of β-blockers may improve left ventricular systolic function, which should positively influence DFT by improving the function of the myocardial substrate.

Angiotensin-converting enzyme inhibitors
Angiotensin-converting enzyme inhibitors have evolved as the cornerstone of therapy for patients with systolic dysfunction. Animal studies have demonstrated no significant change in DFT after administration of an intravenous angiotensin-converting enzyme inhibitor [74].

Angiotensin II receptor blockers
Angiotensin II receptor blockers are a class of drugs often used in the event that angiotensin-converting enzyme inhibitors are poorly tolerated or contraindicated. In animal studies, angiotensin II receptor blockers showed no significant effect on DFTs [74].

Sildenafil
Sildenafil is a cGMP-specific phosphodiesterase inhibitor, used in the treatment of erectile dysfunction (and, to a lesser degree, in the treatment of pulmonary hypertension). There were hundreds of ‘spontaneous reports of death’ (to the US FDA) in patients who had received sildenafil [75]. In an animal study, at supratherapeutic doses, sildenafil was found to increase DFT [76]. As of the writing of this review, most of the experience with sildenafil has been in the treatment of erectile dysfunction. In the treatment of erectile dysfunction the drug is used sporadically at a recommended starting dose of 50 mg, with a maximum recommended dose of 100 mg. The use of sildenafil has been expanded to the treatment of pulmonary hypertension. This is a daily use of the medication with a maintenance dose of 20 mg three times daily. The practitioner should be aware of the increased possibility of an elevation of DFT in a patient on a daily dose of the medication.

Fentanyl
Fentanyl is an opioid analgesic, commonly used at the time of ICD implantation. Fentanyl is generally recognized as a safe drug to use in cardiac patients, with no effect on the electrophysiological properties of the heart. Administration of fentanyl, in addition to N2O, was found to elevate DFT [77].

Halothane and isoflurane
Halothane and isoflurane are volatile anesthetic agents used in general anesthesia. Studies have revealed that these two drugs increase DFT during ICD implantation [78].

Verapamil
Verapamil is a class IV antiarrhythmic agent, with calcium channel-blocking effects. As mentioned earlier, the expectation of a calcium channel-blocking drug would be that it would raise DFT. In animal studies, verapamil has significantly increased DFT [64].

Ethanol
The patient, the physician and allied healthcare professionals often do not consider alcohol ingestion as potential drug toxicity. In a porcine animal study, infusion of ethanol significantly elevated the DFT [79]. A case of ineffective ICD therapy, due to excessive whiskey intake, has been cited in the literature [80]. The authors of this report concluded that “excessive alcohol intake may render ICD therapy ineffective in patients with dilated cardiomyopathy and life-threatening ventricular arrhythmias”.

Catecholamines
Epinephrine increases DFT. Epinephrine and norepinephrine effects on DFT were tested showing that norepinephrine reduces DFT while epinephrine has no effect on DFT. This reduction in DFT was attributed to the α1- and β1-agonist properties of norepinephrine [80].

In summary, the drugs that may significantly increase DFT include mexiletine, verapamil, fentanyl, ethanol and the volatile anesthetics, halothane and isoflurane. Sildenafil, in supratherapeutic doses, also demonstrated a significant increase in DFT. The drugs that may significantly decrease DFT include intravenous amiodarone, sotalol, dofetilide and bretylium. Of the former group, the most important agents are amiodarone and verapamil, which are commonly used in clinical practice. These medications may be added to the patient’s drug regimen at any point after the ICD insertion.

Sildenafil may have been the cause of the problem in the patient described in the clinical vignette. In general, one should question drug interaction with DFT whenever there is an abrupt change in DFT. One should withdraw the offending agent and retest DFT to confirm stability. As for fentanyl, halothane and isoflurane, the implanter should be aware of the potential for elevation of DFT. It may be prudent to retest following washouts of these agents. Lastly, it would be wise to advise our patients to avoid excess alcohol intake also. Box 2 summarizes the effects of the discussed pharmacologic agents on DFT.

Conclusion
Although the number of high DFT patients is relatively small with expanded indications for ICD implantation, this number will undoubtedly increase. This review attempted to give the reader an understanding of VF and defibrillation, with a description of the important electrical determinants of defibrillation. In addition, we have described a course of action that can achieve a satisfactory safety margin in the majority of these patients.

Expert commentary & five-year view
Improving defibrillation effectiveness
The effectiveness of the current generation of defibrillators is satisfactory, yet in selected population of patients with high DFT, the safety margin is very narrow. The availability of additional
waveform programming options, as well as the possibility of the development of new, more complex waveform morphologies, such as parallel-series waveforms or triphasic waveforms, may certainly achieve more effective defibrillation with lower energy requirements. This will not only improve the safety and effectiveness of the device, but will also positively influence the longevity of the battery.

**Painless therapy**
Currently, ICD shock therapy remains very painful, and multiple ICD shocks can be psychologically traumatizing. Anti-tachycardia-pacing certainly can be extremely effective in terminating ventricular tachycardia, even for those that are very fast. Ongoing research is also exploring new waveform designs that can potentially produce less painful shocks.

**Lead design**
Recent troubles with lead reliability, as well as with ventricle perforations, have profoundly affected the reliability of ICD systems. The ongoing effort is focusing on the design of a small-diameter lead that can perform reliably over the long term. Potential size reduction, as well as changes in coil design, will hopefully improve not only reliability, but also allow for easier extraction of the lead. The impending launch of the leads with a coaxial connector (IS-4 connector) will decrease pocket bulk and eliminate mistakes with coil connections. Improvement in implant techniques, including septal placement of the leads, will also afford lower frequency of ventricular perforation.

**Leadless ICD**
Leadless ICD systems will ultimately eliminate all complications associated with the implant of intravascular devices. Without a doubt, it will also create new problems since the new defibrillation leads will still be exposed to mechanical stress. The sensing in these systems will have its own challenges since sensing of myopotentials and external interference may result in inappropriate shocks.

As much as the technology improvements are making ICD therapy safe and effective, one of the greatest challenges that the electrophysiological community is facing is therapy awareness. Depending on estimates, even with the most optimistic outlook, only approximately 40% of eligible patients receive device implants. A concerted effort is needed to educate the medical community and patients regarding the benefits of defibrillator therapy.

**Key issues**
- The treatment of patients with high defibrillation threshold (DFT) at the time of implantation includes ruling out pneumothorax and verifying that the leads are in the correct position.
- Several factors influence the stability of the DFT over time. The most important factors affecting DFT drift include the specific lead system utilized and the defibrillation waveform.
- DFT drift over time occurs partly due to changes between the electrodes and surrounding tissue, which can contribute to increased energy requirements. Changes in myocardial substrate over time, possibly due to disease progression, may also significantly contribute to an upward DFT shift.
- Following the implantation of an ICD, many patients will have their medication changed. Drugs can either lower or raise the DFT, and medications can even be used to optimize DFTs when all other options have been exhausted.
- New leadless and lead ICD systems are continually being developed but one of the greatest challenges that the electrophysiological community is facing is therapy awareness.
- Patients with nonischemic cardiomyopathy tend to have a high DFT.
- Aggressive heart failure management may lower the DFT.
- The majority of patients with high DFT can be managed with noninvasive measures.
- DFT testing may carry nontrivial morbidity and mortality.

**Box 2. Effect of pharmacologic agents on defibrillation threshold.**

<table>
<thead>
<tr>
<th>Raises DFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fentanyl†</td>
</tr>
<tr>
<td>- Halothane‡</td>
</tr>
<tr>
<td>- Isoflurane‡</td>
</tr>
<tr>
<td>- Mexiletine‡</td>
</tr>
<tr>
<td>- Sildenafil‡</td>
</tr>
<tr>
<td>- Ethanol‡</td>
</tr>
<tr>
<td>- Verapamil‡</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lowers DFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sotalol†</td>
</tr>
<tr>
<td>- Dofetilide§</td>
</tr>
<tr>
<td>- Norepinephrine§</td>
</tr>
<tr>
<td>- Amiodarone (intravenous)*</td>
</tr>
<tr>
<td>- Bretylium§</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No effect on DFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Propranolol†</td>
</tr>
<tr>
<td>- ACE inhibitors†</td>
</tr>
<tr>
<td>- ARBs†</td>
</tr>
<tr>
<td>- Epinephrine†</td>
</tr>
</tbody>
</table>

*Supported by data from a randomized clinical trial.
†Supported by a case report.
‡Supported by manufacturers recommendation.
§Supported by animal studies.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin II receptor blocker; DFT: Defibrillation threshold.
Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
No writing assistance was utilized in the production of this manuscript.

References
Papers of special note have been highlighted as:
• of interest

** of considerable interest


** Brings attention to significant morbidity and mortality associated with defibrillation threshold (DFT) testing.


** Reassuring data showing that patients with high DFT do not have an increased long-term mortality.


Management of high defibrillation threshold

Review


45 Thakur RK, Souza JJ, Chapman PD et al. Electrode polarity is an important determinant of defibrillation efficacy using a nonthoracotomy system. PACE 17, 919–923 (1994).


66 Hohnoser SH, Dorian P, Roberts R et al. Effect of amiodarone and sotalol on ventricular defibrillation threshold: the

• Refutes effects of amiodarone on DFT.


Website


Affiliations

• Eric R Uyguanco, MD Clinical Cardiac Electrophysiology Fellow Electrophysiology Section, Division of Cardiovascular Medicine, Department of Medicine, University Hospital of Brooklyn, State University of New York, Downstate Medical Center, 445 Lenox Road, Brooklyn, NY 11203, USA Tel.: +1 718 270 4147 Fax: +1 718 270 4106 ericuyguanco@yahoo.com

• Aaron Berger, MD Clinical Cardiac Electrophysiology Fellow, Electrophysiology Section, Division of Cardiovascular Medicine, Department of Medicine, University Hospital of Brooklyn, State University of New York, Downstate Medical Center, 445 Lenox Road, Brooklyn, NY 11203, USA Tel.: +1 718 270 4147 Fax: +1 718 270 4106 docberger@hotmail.com

• Adam S Budzikowski, MD, PhD Assistant Clinical Professor of Medicine, Electrophysiology Section, Division of Cardiovascular Medicine, Department of Medicine, University Hospital of Brooklyn, State University of New York, Downstate Medical Center, 445 Lenox Road, Brooklyn, NY 11203, USA Tel.: +1 718 270 4147 Fax: +1 718 270 4106 adam.budzikowski@downstate.edu

• Moshe Gunsburg, MD Brookdale University Medical Center, 1 Brookdale Plaza, Brooklyn, New York, NY 11212, USA Tel.: +1 718 240 6288 mgunsbur@brookdale.edu

• John Kassotis, MD, Eng. Sci. D Director of Clinical Cardiac Electrophysiology Service, Director of the Clinical Cardiac Electrophysiology Fellowship Program, Associate Clinical Professor of Medicine, Electrophysiology Section, Division of Cardiovascular Medicine, Department of Medicine, University Hospital of Brooklyn, State University of New York, Downstate Medical Center, 445 Lenox Road, Brooklyn, NY 11203, USA Tel.: +1 718 270 4147 Fax: +1 718 270 4106 jtk747@aol.com