

# The pharmacology of electrical stimulation in the heart: Where devices meet drugs

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**Both cardiac electrical stimulation and cardiac pharmacological agents exert effects by acting upon ion channels, secondary messengers and autonomic nerve terminals. Defining the common substrates between devices and drugs provides the evaluation tools to warn of unsafe interactions with pacemakers, defibrillators or detection of cardiac arrhythmias. This review describes substrates of drug-device interaction, reviews research on drug-like effects of devices, and provides a framework for how the physiology of interaction translates to streamlined clinical trials.**

## Introduction

Cardiac stimulation devices (defibrillators, pacemakers, and others) are given to patients with underlying cardiomyopathies. These patients also receive pharmacotherapy for their underlying conditions. Given the number and combination of concomitant medications, devices cannot reasonably be tested in the clinic for interaction. This would be especially true for implantable cardioverter defibrillators (ICDs), because ventricular fibrillation is an unusual event. We also know that drugs will alter defibrillation thresholds, pacing thresholds, ionotropicity and electrocardiographic waveforms. These drug-related effects also would alter the efficacy and even the ability of the cardiac devices to detect arrhythmias. Similarly, electrical defibrillation may affect autonomic

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neurotransmitter release and muscle function. This article is a conceptual review of the modes and mechanisms by which these interactions can occur. Some of the potential interactions specific for ICDs have been cited by the American Heart Association [1] and reviewed by Brode *et al.* [2] and Swerdlow and Friedman [3,4]. To date the main concern has been the potential for drugs to elevate defibrillation and pacing thresholds, which decreases the efficacy of ICDs and pacemakers. A potential exists for other interactions, and these merit investigation.

## Interaction between devices and drugs – key technologies

### Voltage-sensitive channels

Cardiac electrical stimulation devices, namely defibrillators and pacemakers operate by passing electrical current in the heart. The electrical current is intended to activate voltage sensitive ion channels in cardiac tissue to induce action potentials, in the case of pacemakers, or block the aberrant propagation of action potentials, in the case of defibrillators. The electric current charges the membrane in a time-dependent fashion, and both the activation and inactivation of ion channels are time dependent. There are a variety of channels for sodium, calcium, potassium and chloride. Each channel type has its own voltage sensitivity and time dependence. The

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**Table 1. Types of Interactions between Drugs and Cardiac Electrical Devices**

	Substrate of interaction	Examples
<b>Drug effects upon device</b>		
Defibrillation threshold change	Voltage-sensitive channels, cytosolic calcium	IA, IB, IC, II [1–4,6,7,20]
Pacing threshold change	Voltage sensitive ion channels	IC, II [2]
Failure to defibrillate	Death from increased DFT	(Same as DFT change above) [2–4,20,21]
Failure to detect arrhythmia	Slowed rate of VT or diminished electrogram amplitude or morphology change	IA, IC, II [2–4,20]
Inappropriate shock	altered morphology of electrogram – misclassification of SVT as VT, increased ventricular rate from slowed atrial fibrillation with nodal conduction	IC [2,4,19,20]
2° arrhythmia induction, including refrillation	Elevated calcium, long QT	(Area of research) [9,12,21]
<b>Drug-like effects of devices</b>		
Cytosolic calcium changes	Ion channel changes electroporation	Strong defibrillator shocks, CRT, systolic pacing [9–12]
Changes in autonomic function	Depolarization of autonomic nerve terminals in the heart	CRT, defibrillator shocks [11,13,14,18]
Remodeling in heart failure	Resynchronization of mechanical and electrical activity	CRT [22,24]

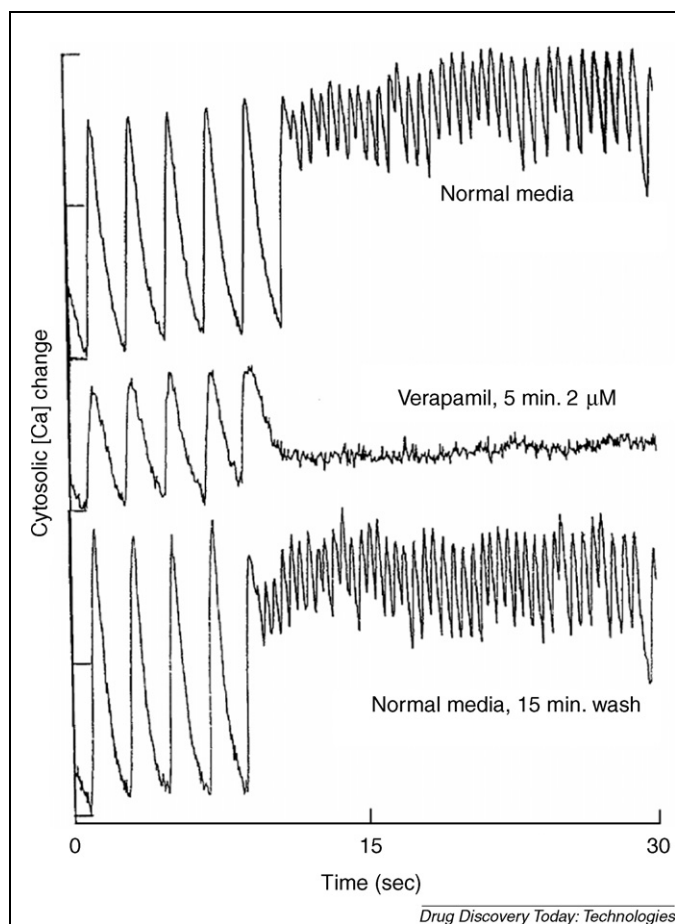
regions of the myocardium specialized for pacemaker activity, rapid conduction, slow conduction and delayed conduction have various blends for channel types and densities suited for these functions. The specific ion channels and their properties have been reviewed by Katz [5]. In evoking a cardiac action potential, electric current depolarizes the cell which causes a rapid influx of sodium ions to produce the steep depolarization of the action potential, this is followed by calcium and slower sodium channel activation, which produces the plateau phase of the action potential in which the inward current is balanced by an outward current of potassium and chloride. During the repolarization phase the outward current becomes greater than the inward current, and the membrane potential returns to resting.

Pacemaker devices apply brief low-amplitude current to evoke action potentials in diseased tissue. Pacing is applied to excite a single point, and propagation of action potentials propagates from that point. Defibrillation involves the use of stronger currents to block advancing aberrant action potentials so that a normal rhythm can take over. In defibrillation, current polarizes cells through the entire heart which is followed by a period of refractoriness and the normal cardiac pacemaker tissue re-initiates a rhythm. Therefore, drugs that alter excitation would affect defibrillation.

Table 1 summarizes the effects of drug-device interactions and the substrates of these interactions, based upon the types of drugs. For example, the Vaughan Williams classification of antiarrhythmic drugs (see [5]) classifies sodium channel blockers into Class I. Accordingly, the effect of lidocaine, a relatively pure fast sodium channel blocker (Class IB), is to raise defibrillation energy requirements [6]. This probably occurs because of a slowing in cardiac conduction which increases action potential dispersion. Similarly, the volatile

anesthetics halothane and isoflurane raise defibrillation threshold (DFT) [7]. The other classes are for  $\beta$ -adrenergic blockers (Class II, see below), potassium channel blockers (Class III, e.g. amiodarone), and calcium channel blockers (Class IV, e.g. verapamil). A more recent example of drug interactions with defibrillation is from a randomized study of defibrillation resistant patients; Dorian *et al.* [8] showed better resuscitation survival with intravenous amiodarone than lidocaine.

Calcium acts both as an ion carrying charge as part of the action potential signal and as a secondary messenger to control contraction. Calcium ions enter the cytosol through the plasma membrane and are released from intracellular stores contained in the sarcoplasmic reticulum. Many drugs affect the release and re-uptake of calcium from both sites. Electrical stimulation of the heart also affects cytosolic calcium. In our work, we have shown that defibrillation shocks can elevate cytosolic calcium, which remains high during a post-shock arrest period [9]. A prolonged post-shock arrest and elevated calcium are biomarkers for unsuccessful defibrillation and causal of refrillation [10,11]. We have also shown that this effect is sensitive to the defibrillation waveform applied [12]. In organotypic heart cell aggregates, we found that the calcium channel blocker verapamil (Class IV) prolongs the post-shock arrest [13]. In addition, verapamil reversibly lowers cytosolic calcium level during the post-shock arrest period (Fig. 1); whereas ryanodine increases and prolongs the calcium transient. The seemingly paradoxical effect of verapamil (i.e. lowering calcium and prolonging arrest) may be because of verapamil blocking calcium entry which leads to a secondary decrease in calcium-activated potassium channels [5]. Diminished activation of these channels would prolong the post-shock depolarization.



**Figure 1.** Calcium channel blocker decreases cytosolic calcium following defibrillation shock. The upper trace shows an optical recording of calcium changes in aggregate of cultured myocardial cells from chick embryo [9,13,24] when a 56 V/cm defibrillator shock is applied at 13 s. The result is that cytosolic calcium remains at systolic levels. The effect of 2  $\mu$ M verapamil for 5 min brings the post-shock calcium level to diastolic values (middle trace). The effect is reversible with a wash-out (lower trace). This demonstrates that calcium entry following a defibrillator shock is through the L-type calcium channel. Thus drugs that affect this channel affect defibrillation.

#### Autonomic control

Autonomic innervation of the heart controls heart rate, conduction and contractile function. Autonomic function is mediated via secondary messengers (e.g. cAMP, cGMP, NO) that also regulate calcium. There are two ways cardiac electrical stimulation devices may interact with autonomic function and drugs. The first includes the effects of autonomic drugs on cardiac electrophysiological devices. These effects include a decrease in defibrillation threshold with sympathetic stimulation or beta agonists and reversal of the effect with  $\beta$ -blockade [14]. In our work we also found that adrenergic agonists decrease the duration of arrest following defibrillation shocks, which is a biomarker favorable for defibrillation success [13]. This may be part of mechanism for the success of epinephrine during resuscitation. The second source of interaction is the effect of cardiac stimulation and defibrillation upon the innervation of the heart, for

example, the observed decrease in cardiac norepinephrine following cardiac defibrillation [15]. The cause of this effect is not known, but the authors speculate that it may be part of the reason for post-shock depression of cardiac activity. In skeletal muscle, electrical stimulation activates nerve terminals at lower threshold than for the direct activation of muscle [16]. A defibrillation shock could produce electroporation at nerve terminals [17] that would lead to the block of cholinergic and adrenergic neural activity. However, the system is complex because of the combination of sympathetic, parasympathetic, myelinated, unmyelinated afferent and efferent nerve fibers that exist in the heart at different locations [18]. The effects of electric shocks upon this innervation have not been well studied, but this is a prime area where both drugs and electric stimulation will interact with physiology.

#### Effect on device signal detection

The function of cardiac electrical stimulation devices depends upon the ability to sense electrocardiographic waves. Drugs that affect the temporal or amplitude components of these waves may produce unintended effects resulting in inappropriate function of the devices. One example cited by Brode *et al.* [2] is the prolongation of ventricular tachycardia (VT) cycle length by drugs that would affect rate-sensitive detection. Swerdlow and Friedman [3,4] recommend changing ICD settings for longer VT cycle lengths. They also review effects of drugs upon electrogram morphology, and note that some detection algorithms depend upon morphology templates. Swerdlow and Friedman [4] also describe the drug-induced elevation in defibrillation threshold as a life-threatening interaction, and therefore recommend an energy safety margin to protect against this effect.

#### Drugs and inappropriate ICD shocks

The effects of drugs upon device function include the inappropriate delivery of ICD shocks, that is, shocks when the patient is not suffering cardiogenic symptoms. In one large-scale study, 22% of ICD shocks were inappropriate [19]. Major causes of inappropriate shocks are supraventricular tachycardia (SVT) and oversensing of T-waves [20]. As described, antiarrhythmic medications can promote these effects. The well-known significance of inappropriate shocks is the effect upon quality of life. Physiological effects of such shocks are not well understood, but these may include post-shock arrhythmias [21] and changes in autonomic function in the heart [2]. In a review, Gehi *et al.* [20] compared the effectiveness of antiarrhythmics in reducing inappropriate shocks, all-cause shocks, and survival. Some drug agents and combinations appear to reduce both inappropriate shocks and prolong survival. Therefore the interactions between drugs and ICDs also promote positive outcomes.

### Cardiac stimulation devices for heart failure

Most cardiac devices are intended to have acute and direct electrical effects, for example, activation of cardiac excitation or the block of fibrillating waves. However, there are two devices that are intended to have long-term drug like effects for the treatment of heart failure. (Heart failure is when the heart cannot pump enough blood to supply the needs of the body.) Heart failure follows a course of steady decline as the heart remodels during the illness. Many drugs are used in the treatment including diuretics, endocrine disrupters and  $\beta$ -blockers. Interestingly, positive inotropic agents cannot be used because following an initial improvement, there is high mortality; however,  $\beta$ -blockade will produce long-term improvements in cardiac function.

Cardiac resynchronization therapy (CRT) has been approved for the treatment of heart failure. This therapy is used in patients with conduction disturbances in the heart (e.g. bundle-branch block) and the sequence of contraction is disturbed. CRT is also responsible for a beneficial reverse remodeling of the heart, in which contractile function improves [22]. The cause of this long-term improvement in intrinsic contractile function is not known, but it is an effect that is complementary to  $\beta$ -blockade. Another proposed electrical stimulation method for improving myocardial function during heart failure is by means of electrical stimulation during systole. This stimulation may elevate cytosolic calcium levels and increase contractility [23]. The mode of action of this device is still under investigation. The devices have been reported to induce a reverse remodeling of the heart [24].

### Impact upon product development

It is clear that both devices and drugs have common substrates of action and therefore interactions are likely. Some known interactions have been discussed and others are not well understood. With over 150,000 ICDs implanted in the U.S. annually, the long term effects of defibrillation shocks upon ion channel kinetics, calcium dynamics, and autonomic nerve terminals need particular study. The immediate benefits of research concerning mechanisms of interaction would be to focus clinical trials (see Table 2). Patients with defibrillators usually have several concomitant medications,

and clinical trials for defibrillators are limited in patient number, and often study subjects do not receive therapeutic shocks. Therefore, it is unlikely that those clinical trials will uncover interactions. Similarly CRT and pacemakers are given to patients with concomitant medications and have limited trials. Knowledge of interaction would help focus clinical premarket, and potential drug-device interaction would then be noted in product labeling. For postmarket reports, the collection of information concerning concomitant drugs and devices would be helpful for suggesting whether interactions occurred that may have affected patient outcome.

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**Table 2. Impact of drug-device interactions upon product development**

Preclinical testing for interactions – research on likely interactions
Focused premarket clinical testing – focus premarket clinical testing strategically
Labeling – caution regarding likely interactions, especially when patients change drugs
Focused postmarket analysis – collect information on concomitant medications in adverse events reporting

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