Effects of Class III Antiarrhythmic Drugs on Biphasic Shock Efficacy in Humans

B. MERKELY, A. LUBINSKI[1], O. KISS, L. GELLÉR, T. GYÖNGY, E. LEWICKA-NOWAK[1], F. HORKAY, G. SWIATECKA[1], J. PILZ[2], M. SCHALDACH[2]
Semmelweis University, Budapest, Hungary
[1]University Gdansk, Poland
[2]University Erlangen-Nürnberg, Germany

Summary

The biphasic waveform and antiarrhythmic drugs are known to influence defibrillation efficacy. However, the optimal biphasic waveform for 2nd phase duration in man has not yet been defined. In a multicenter, randomized and prospective study, the defibrillation efficacy of 2 msec vs. 5 msec 2nd phase duration of biphasic pulses using two 100 µF capacitors was compared in 62 patients (age: 54 ± 13 years, male: 74%, CAD: 60%, DCM: 19%, EF: 43 ± 17%, amiodarone: 47%, d,l sotalol 13%) with a unipolar pectoral transvenous defibrillation system (RV-E vs. can; fractally coated SPS-lead vs. Phylax 06 or XM active housing, Biotronik). The 1st phase parameters for both biphasic waveforms were as follows: charging voltage 100%, switching voltage 40%. Defibrillation threshold (DFT) was determined in a random order with either 2 msec or 5 msec second phase tested first during ICD implantation. Results: significant difference was found in stored energy at DFT between 2 msec and 5 msec 2nd phase duration pulse form (9.5 ± 0.6 vs. 11.3 ± 0.7 p < 0.01). In subgroup analysis in patients treated with class III drugs, such as amiodaron or d,l sotalol, there was a markedly significant difference between DFTs with shocks of longer or shorter 2nd phases, but in the control group there was no difference. Conclusions: Chronic amiodarone treatment increases DFT using biphasic shock only with the longer second phase duration. In patients treated with class III drugs, DFT is significantly lower with shorter second phase duration.

Key Words

ICD, class III antiarrhythmic drugs, biphasic shock efficacy

Introduction

To defibrillate with a low amount of energy, the potential field generated by the defibrillating shock must be optimized. The potential gradient has been reported to be closely related to the success or failure of defibrillation. The defibrillation threshold (DFT) is known to depend on parameters of the defibrillation system and on clinical characteristics of the patient. These parameters of the defibrillation system are lead configuration, electrode quality, and shock waveform. The primary hypothesis of biphasic defibrillation is that the first phase leaves a residual charge on the membranes of the myocites, which can then reinitiate fibrillation. The second phase diminishes this charge, reducing the potential for refibrillation [9]. Pulse duration, tilt and amplitude of each phase of the biphasic waveform are known to influence defibrillation efficacy [6]. Due to the previous results of a quantitative cellular model the optimal second phase duration appears to be about 2.5 msec [9]. Experimental studies have shown that biphasic waveform with a second phase of shorter duration and lower amplitude are more efficacious [1,8,11,18]. Interactions of ICDs and, class III anti-arrhythmic agents - frequently used in this patient group - are of great importance. D,l sotalol treatment has been associated with a decrease in DFT in both animal and clinical studies [2,19], whereas amiodarone has been reported to have a variable effects on the DFT. Its effects differ according to the length, way of administration, shock waveform, and lead configuration [3,4,5,7,10].

number of patients	62
gender	26 % females 74 % males
age years	54 ± 13 (range 23 - 73)
weight	76 ± 12 kg
ejection fraction	43±17 %
NYHA class	I - 40%, II - 45%, III - 15%

Table 1. Patient data I.

The effect of shorter second phase duration of the biphasic waveform using smaller output capacitors and unipolar lead configuration in patient subgroups with different underlying diseases and antiarrhythmic medication has not yet been defined.

Materials and Methods

In this multicenter study the used unipolar lead system consists of an 11 French tripolar shock-pacing-sensing right ventricular-electrode (SPS RV-electrode) and the active housing of the Phylax 06 or XM ICD. The device can easily be implanted in the left pectoral region. The surface of our transvenous electrodes is coated with fractally structured iridium. The fractal iridium coating enlarges the active surface of the electrodes more than 1000-fold thereby increasing the Helmholtz capacitance [12,13].
The specific purpose of this clinical study was to evaluate the effect of shortening the second phase of the biphasic pulse form on the DFT applying the clinically most frequently used unipolar configuration under different clinical circumstances especially antiarrhythmic medication.

Subjects
The randomized and prospective study was performed in two centers: in the Department of Cardiovascular Surgery of the Semmelweis Medical University in Budapest, Hungary and in the Dept. of Cardiology of the Medical University of Gdansk, Poland.
The data concerning the 62 patients are shown on Tables 1 and 2.

Defibrillation protocol
The defibrillation efficacy of 2 msec vs. 5 msec second phase duration of biphasic pulses using two 100 μF capacitors was compared using an unipolar pectoral transvenous defibrillation system.

Primary cardiac diseases:		
Coronary artery disease	37	60%
Nonischemic cardiomyopathy	10	16%
Primary electrical disease	8	13%
Hypertrophic cardiomyopathy	3	5%
Indications:		
VT	22	35%
VT+VF	25	40%
VF	15	24%
Medication:		
amiodarone	29	47%
d,l sotalol	8	13%
beta-blocking agent alone	13	(21%)

Table 2. Patient data II.

The first phase parameters for both biphasic waveforms were as follows: charging voltage 100%, switching voltage 40%. The initial phase was positive, that means anodal biphasic shocks were delivered. Defibrillation threshold (DFT) was determined in a random order with either 2 msec or 5 msec second phase tested first in each patient (Figure 1).
Ventricular fibrillation was induced using a short burst of 50 Hz alternating current or a T-wave induction shock. After 10 seconds of fibrillation defibrillation was attempted by applying the biphasic defibrillation shock. Fibrillation-defibrillation sequences were performed every 5 minutes.
DFT determination was performed using a binary search protocol during ICD implantation. The first test-

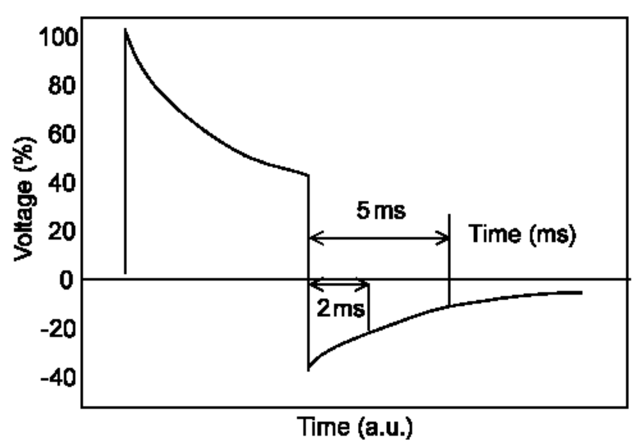

Figure 1. Morphologies of the delivered shocks.

2nd phase dur.	Charging voltage (V)	Stored energy (J)	Delivered energy (J)	Impedance (Ω)
2 msec	423 ± 108	9.5 ± 4.5	8.7 ± 4.1	70 ± 10
5 msec	463 ± 113	11.3 ± 5.2	10.9 ± 4.9	69 ± 10
p value	p<0.001	p<0.001	p<0.001	NS.

Table 3. Charging voltage energy and impedance at DFT in n = 62 patients (mean ± SD).

ed charging voltage was 500 V, which equals 13 Joules. DFT was defined as the lowest charging voltage or energy effective for defibrillation. If a defibrillation shock failed, a rescue shock of 40 J was delivered. Minimal implantation criteria required two consecutive successful conversions of ventricular fibrillation using 21 Joules or less.

In all patients RV-E vs. active housing configuration in the pectoral region was used. All implantations were performed using only transvenous leads without additional subcutaneous patch or transvenous electrodes.

Statistical analysis

Paired T-test was used to compare defibrillation thresholds with the shorter and longer second phase duration. Independent samples T-test was performed to compare the subgroups.

Results

The overview of the summarized results of the 62 implantations is presented on table 3. The mean shock impedance was 70 Ω. A significant difference was found in charging voltage, stored, and delivered energy at DFT between 2 msec and 5 msec 2nd phase duration pulse forms using 100 µF capacitance. The mean charging voltage was 462.9 V using shocks with 5 msec and 423.4 V with 2 msec second phase duration. The mean delivered energy at defibrillation threshold was 10.9 J using 5 msec, and 8.7 J with 2 msec second phase waveforms (Table 3). The subgroup analysis also showed significantly lower DFTs with the shorter second phase pulse forms in patient groups with low or high ejection fraction, low or high shock impedances and different NYHA classes.

The significant difference was also found in subgroups with different diseases, eg. CAD or DCM subgroups. Interestingly, in the patient group without structural heart disease (primary electrical disease) no significant difference was found between DFT-s with 2 or 5 msec second phase shocks. This subgroup mostly had no antiarrhythmic medication.

The most interesting observation of the subgroup analysis was that in patients treated with class III drugs, such as amiodaron or d,l sotalol, there was markedly significant difference between DFTs with shocks of longer or shorter second phases (Figure 2). On the contrary, in the control group (without amiodarone and sotalol) we have not found any significant differences (Figure 2). That means lengthening the repolarisation phase of the action potential and the refractory period reinforces the beneficial effects of applying biphasic shocks with shorter second phases. However, the underlying mechanisms are unknown. Patients treated chronically with amiodarone had a significant higher DFT with the biphasic shock using 5 msec second phase duration than patients without

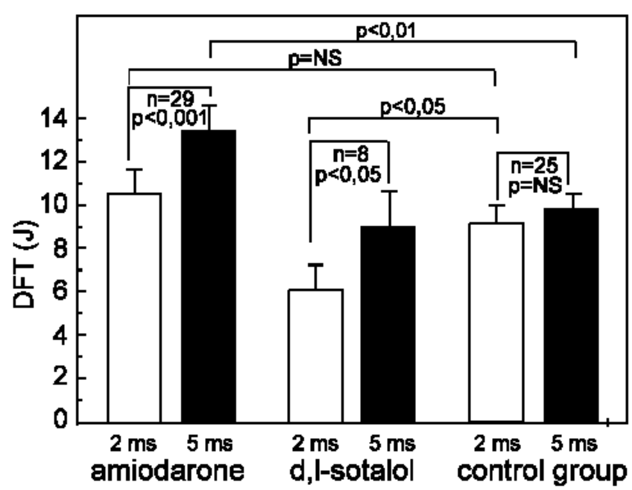

Figure 2. Defibrillation thresholds of patient subgroups treated with amiodarone, sotalol and the control group delivering biphasic shocks with 2 and 5 msec long second phases.

antiarrhythmic drugs, but using the shorter second phase duration there was no significant difference. D, l sotalol treatment decreased the DFT significantly using the shorter second phase duration.

Conclusions

Biphasic shocks with either 2 msec or 5 msec second phase duration applied over endocardial fractally iridium-coated shock electrodes in unipolar configuration can defibrillate with low total energy. Biphasic waveform with shorter second phase duration is more efficient in patients treated with class III AA-drugs [14]. Drugs lengthening the repolarisation phase may reinforce the beneficial effects of applying biphasic shocks with shorter second phases. Chronic amiodarone treatment increases DFT using biphasic shocks only with the longer second phase duration. Our results also support previous data that D,l sotalol treatment decreases the DFT. The clinical reports of Natale, Swerdlow and Swartz can support our results by showing that biphasic waveforms of shorter tilt can provide lower DFT-s than biphasic waveforms of longer tilt in human [15,16,17].

The optimization of the shock waveform might offer the opportunity to extend the battery life of the cardioverter defibrillator unit and reduce the time of charging the shock capacitors and the amount of possible myocardial damage.

References

[1] Adams TP, Leonelli FM, Brewer JE, et al. A short duration, small capacitor biphasic waveform has lower thresholds than the clinically available biphasic waveform (abstract) PACE. 1995; 18: 1789.

[2] Dorian P, Newman D, Sheahan R, et al. d-Sotalol decreases defibrillation energy requirements in humans: a novel indication for drug therapy. J Cardiovasc Electrophysiol. 1996; 7: 952-61.

[3] Frame LH. The effect of chronic oral and acute intravenous amiodarone administration on ventricular defibrillation threshold using implanted electrodes in dogs. Pacing Clin Electrophysiol. 1989; 12: 339-46.

[4] Guarnieri T, Levine JH, Veltri EP, et al. Success of chronic defibrillation and the role of antiarrhythmic drugs with the automatic implantable cardioverter/defibrillator. Am J Cardiol. 1987; 60: 1061-1064.

[5] Huang SK, Tan de Guzman WL, Chenarides JG, et al. Effects of long-term amiodarone therapy on the defibrillation threshold and the rate of shocks of the implantable cardioverter-defibrillator. Am Heart J. 1991; 122: 720-727.

[6] Irnich W. Optimal truncation of defibrillation pulses. PACE. 1995; 18: 673.

[7] Jung W, Manz M, Pizzulli L, et al. Effects of chronic amiodarone therapy on defibrillation threshold. Am J Cardiol. 1992; 70: 1023-1027.

[8] Kiss O, Merkely B, Gellér L, et al. Experimental study for pulse optimisation of the defibrillating shock (abstract) Cardiologia Hungarica. 1997; 26 (Suppl. 3.): 36.

[9] Kroll MW. A minimal model of the single capacitor biphasic defibrillation waveform. PACE. 1994; 17: 1782-1792.

[10] Manz M, Jung W, Lüderitz B. Interactions between drugs and devices: experimental and clinical studies. Am Heart J. 1994; 127: 978-984.

[11] Matula MH, Brooks MJ, Pan Q, et al. Optimization of total pulse duration and second (negative) pulse duration of biphasic waveform for ventricular defibrillation (abstract). PACE. 1993; 16: 258.

[12] Merkely B, Kékesi V, Gyöngy T, et al. Results of an experimental in vivo study using new endocardial electrodes with low transvenous defibrillation threshold. PACE. 1995; 18: 1155.

[13] Merkely B, Kékesi V, Vecsey T, et al. Fractally coated endocardial electrodes: a new approach for low defibrillation threshold. New Trends in Arrhythmias. 1995; 11: 763.

[14] Merkely B, Lubinsky A, Gyöngy T, et al. Shortening of the second phase duration improves biphasic defibrillation efficacy in humans. JACC. 1998; 31 (5): 319C (abstract).

[15] Natale A, Sra J, Krum D, et al. Relative efficacy of different tilts with biphasic defibrillation in humans. PACE. 1996; 19: 197.

[16] Swartz JF, Fletcher RD, Karasik PE. Optimization of biphasic waveforms for human nonthoracotomy defibrillation. Circulation. 1993; 88: 2646-2654.

[17] Swerdlow CD, Kass RM, Davie S, et al. Short biphasic pulses from 90 Microfarad capacitors lower defibrillation threshold. PACE. 1996; 19: 1053.

[18] Tang ASL, Yabe S, Wharton JM, et al. Ventricular defibrillation using biphasic waveforms: The importance of phasic defibrillation. J Am Coll Cardiol. 1989; 13: 207-214.

[19] Wang M, Dorian P. DL- and D-sotalol decrease defibrillation energy requirements. Pacing Clin Electrophysiol. 1989; 12: 1522-1529.