The Impact of Catecholamines in Patients with or without Beta-Blockers on the Ventricular Fibrillation Cycle Length and Ventricular Fibrillation Cycle Length Variability

Bokyoung Min, Pharm.D., Jeffrey Kluger, M.D., James S. Kalus, Pharm.D., Danette Guertin, A.R.N.P., Brian F. McBride, Pharm.D., and C. Michael White, Pharm.D.

From the Divisions of Drug Information and Cardiology, Hartford Hospital, Hartford, CT and the University of Connecticut School of Pharmacy and Medicine, Storrs and Farmington, CT

Objectives: To evaluate the impact of epinephrine, norepinephrine, or placebo on the ventricular fibrillation cycle length (VFCL) and the variability of VFCL (cvVFCL) measurements in implantable cardioverter defibrillator (ICD) patients with or without beta-blockers.

Methods: Forty-three patients scheduled for their 6-week post-ICD placement noninvasive electrophysiologic study were included in the study at the Arrhythmia Procedure Laboratory at Hartford Hospital, Hartford, CT. This randomized, double-blind, placebo-controlled evaluation was approved by the Hartford Hospital Institutional Review Board.

Results: After 2 seconds of continuous VF, 7 consecutive VFCLs were measured from the ICD device recording printout using a 0.5 mm scale ruler under magnification at baseline and after the infusion of catecholamines (epinephrine or norepinephrine at 2 mcg/min) or matching placebo at steady state. The average VFCL and the cvVFCL were determined for each study phase. Subgroup analysis based on chronic beta-blocker use was performed. No between-group differences were noted for epinephrine, norepinephrine, or placebo group for baseline ($P = 0.538$) or postinfusion VFCL ($P = 0.749$) or for baseline ($P = 0.561$) or postinfusion cvVFCL ($P = 0.623$). Regardless of catecholamine group randomization, longer pre- and postinfusion VFCL were noted in those receiving beta-blockers ($P = 0.157$, $P = 0.019$) but no differences in cvVFCL were noted ($P = 0.216$, $P = 0.474$) versus those without beta-blockers, respectively.

Conclusion: Moderately dosed epinephrine or norepinephrine does not affect either VFCL or the variability of VFCL after short duration of ventricular fibrillation. Chronic cardioselective beta-blockade prolongs VFCL without any impact on coefficient of variation of VFCL.

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VFCL; variability of VFCL; ventricular arrhythmias; implantable defibrillators

Ventricular Fibrillation Cycle Length (VFCL) is a measure of local refractoriness. Interventions that prolong refractoriness without slowing conduction would decrease the frequency of VF by increasing the size of the local wavelets or reentrant rotors.^{1,2} The variability in successive VFCL measurements (determined by the coefficient of variation of VFCL measurements) within an individual has been shown to be an independent pre-

dictor of subsequent recurrent arrhythmias among patients with an implantable cardioverter defibrillator (ICD).³ In addition, greater heterogeneity of VF waves is seen among patients with VF needing ICD termination than patients whose VF terminates spontaneously.⁴

Previous studies evaluated the impact of several drugs on VFCL after a short period of VF as would likely occur in a patient with an ICD

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Address for reprints: C. Michael White, Pharm.D., University of Connecticut and Co-Director, Arrhythmia Research Drug Information Center, Hartford Hospital, Hartford, CT 06102-5037. Fax: 860-545-4371; E-mail: cmwhite@harthosp.org

experiencing VF. Class III antiarrhythmic agents with either beta-blocking (BB, i.e., sotalol) or antiadrenergic effects (i.e., amiodarone) significantly increase the VFCL as does lidocaine (a class Ib agent) without direct adrenergic impact.⁵⁻¹⁰ As such, the direct impact of adrenoceptor agonism or antagonism on VFCL over the short term is unknown.^{9,10}

In a study mimicking out-of-hospital cardiac arrest, swine had VF induced and 10 minutes of continuous VF passed before the intracardiac administration of epinephrine (1mg) or saline.¹¹ In that study, the average VFCL and VFCL variability (VFCL dispersion = maximum VFCL – minimum VFCL) increased continuously over the predrug initiation period in both groups. After the administration of epinephrine, VFCL and the dispersion of VFCL were reduced significantly while continuing to increase in the saline group. While epinephrine demonstrated these effects with long-duration VF, the impact of physiologic catecholamine concentrations of epinephrine or norepinephrine on VFCL or VFCL variability after short-duration VF is unknown. Furthermore, the impact of beta-blockers on VFCL or variability of VFCL measurements with or without catecholamine challenge has not been investigated.

This study evaluates the impact of epinephrine, norepinephrine, or placebo on the VFCL and the variability of VFCL measurements in ICD patients with or without beta-blockers.

METHODS

Patient Population/Drug Regimen

This is a randomized, double-blind, placebo-controlled evaluation approved by the Hartford Hospital Institutional Review Board with written informed consent. Patients scheduled for their 6-week post-ICD placement noninvasive electrophysiologic study (NIEPS) were screened for study entry. Patients were excluded for any of the following reasons: use of drugs with the potential to affect cardiac conduction (monoamine oxidase inhibitors, beta-blockers other than metoprolol or atenolol, alpha-blockers, clonidine, class I or III antiarrhythmic agents, catecholamines, and phosphodiesterase inhibitors), pheochromocytoma, systolic blood pressure >170 mmHg or <90 mmHg, or diastolic blood pressure >100 mmHg or <50 mmHg.

Demographic data were collected during the screening period before randomization. Using

stratified allocation, patients on cardioselective beta-blockers were randomized separately from those without beta-blockers to ensure equal distribution. In both cases, patients were randomized to epinephrine 2 mcg/min, norepinephrine 2 mcg/min, or placebo (equivolume normal saline) groups.

NIEPS Testing/VFCL Determination

Patients were anesthetized with propofol before ICD testing, and computer disks stored all ICD test information. For the baseline test, the first VF episode initiated was used for determining VFCL. The ICD electrocardiogram (tip to ring, Medtronic Inc., Minneapolis, MN; tip to coil, Guidant Corp., St. Paul, MN; Fig. 1) was utilized for VFCL measurements and recorded at the speed of 25 mm/s. Using the computer printout, after 2 seconds of continuous VF, 7 consecutive VFCLs were measured with 0.5 mm scale ruler under magnification. VFCL was defined as the beginning of upstroke from one fibrillatory wave until the beginning of a subsequent upstroke from a subsequent fibrillatory wave. All fractionated wavelets with an amplitude less than 50% of the previous action potential were included in the preceding VFCL measurements.

Subsequent arrhythmia threshold testing occurred using a standard step-down protocol until the failure of defibrillation or 5J defibrillation energy, but no VFCL determinations were made during this period. After a baseline defibrillation threshold was determined, an experimental determination was initiated.

After the completion of baseline protocol, an infusion of one of the three solutions (epinephrine, norepinephrine, or normal saline) was begun and continued until the end of the study. Initiation of VF did not occur until the solutions were infused for 7 minutes to allow epinephrine and norepinephrine to achieve steady state. After the first successful generation of VF, the VFCL was determined as previously described.

The 7 consecutive VFCL measurements for each patient per phase (baseline and postinfusion) were averaged to give the mean VFCL per patient per phase. Then the coefficient of variation of VFCL (cvVFCL) was determined for each patient by using the formula $[(\text{standard deviation of VFCL} \times 100) / \text{a VFCL}]$.

Figure 1. ICD electrocardiograms used for VFCL measurements from Medtronic ICD (A, B) and Guidant ICD (C, D). Baseline (A, C) and post-catecholamine (B, D) VFCLs were measured. An interval between two arrows on each strip represents the example of the VFCL measured.

Table 1. Demographic Characteristics

Characteristic	Epinephrine (n = 14)	Norepinephrine (n = 14)	Placebo (n = 15)
Age	68.2 ± 7.1	65.7 ± 8.7	63.9 ± 10.4
M/F (n)	12/2	8/6	9/6
CAD (%)	92.9	64.3	73.3
DM (%)	28.9	21.4	33.3
REVASC (%)	50.0	28.6	53.3
LVEF (%)	34.4 ± 12.5	37.7 ± 14.2	35.4 ± 11.5
Beta-blockers (n)	10	9	10

M = male; F = female; n = number; CAD = coronary artery disease; DM = diabetes mellitus; REVASC = revascularization; LVEF = left ventricular ejection fraction.

Statistical Analysis

Intergroup VFCL and cvVFCL comparisons were made preinfusion (baseline) and postinfusion using one-way analysis of variance. Significant differences were probed with Bonferroni corrected *t*-tests. Student *t*-tests were used to compare beta-blocker treated patients to non-beta-blocker treated patients within both phases. A *P* value less than 0.05 was considered significant, and all data were presented as means with standard deviations or percentages.

RESULTS

Forty-three subjects were enrolled in the study and had evaluable VFCL data for both study phases. Thirty-six patients had Guidant ICDs (Guidant Corp., St. Paul, MN), while 7 patients had Medtronic ICDs (Medtronic Inc., Minneapolis, MN). Demographic data are summarized in Table 1.

Epinephrine concentrations in the plasma were increased from 56 ± 31 to 615 ± 278 pg/mL ($P < 0.001$) after epinephrine infusion, and norepinephrine concentrations were increased from 594 ± 537 to 1411 ± 673 pg/mL ($P = 0.023$) after norepinephrine infusions. Placebo infusions did not significantly alter epinephrine or norepinephrine infusions.

Preinfusion, there was no difference among the epinephrine, norepinephrine, or placebo groups in baseline VFCL ($P = 0.538$). Regardless of catecholamine group randomization, a trend toward longer preinfusion VFCL was noted among those receiving beta-blockers versus those not receiving beta-blockers (194.4 ± 28.8 vs 182 ± 22.4 ms, respectively, $P = 0.157$). After the infusion

of epinephrine, norepinephrine, or placebo, VFCL was not different between groups (Table 2, $P = 0.749$). Regardless of catecholamine group randomization, significantly longer postinfusion VFCL was noted in those receiving beta-blockers versus those not receiving beta-blockers (Table 3, 200.8 ± 26 vs 181.2 ± 20.4 ms, $P = 0.019$).

The variability of VFCL in each patient was reflected in cvVFCL comparisons. No cvVFCL differences were noted between the three groups prior to infusion ($P = 0.561$) or postinfusion ($P = 0.623$) (Table 2). The use of chronic BB did not alter the cvVFCL either before ($P = 0.216$) or after ($P = 0.474$) the infusions of catecholamines or placebo (Table 3).

The effect of selective beta-blockade on VFCL and cvVFCL in each catecholamine is displayed in Table 4. The study was not powered to detect the differences in these end points and no statistical analysis was performed. Qualitatively, there were no notable differences between the change in VFCL or cvVFCL for epinephrine, norepinephrine, and placebo when they were compared between those with and without beta-blockers.

DISCUSSION

Implications of Altering VFCL

VF becomes sustained by successive reexcitation of multiple wave fronts. As soon as an action potential is repolarized, it is immediately restimulated by one of these wave fronts and the reentrant activation is maintained.⁵ The number of wavelets in the ventricular myocardium during fibrillation is inversely proportional to the refractory period and conduction velocity of the action potential.¹² By prolonging the refractory period, the ventricular

Table 2. VFCL and cvVFCL Comparisons

Group	Epinephrine (n = 14)	Norepinephrine (n = 14)	Placebo (n = 15)	ANOVA
VFCL preinfusion (ms)	183.6 ± 18	194.4 ± 29.2	192.8 ± 32.4	P = 0.538
VFCL postinfusion (ms)	190.8 ± 14	198.4 ± 22.4	194.1 ± 36.1	P = 0.749
Pre- and postinfusion intragroup VFCL <i>t</i> -test	P = 0.248	P = 0.688	P = 0.924	
cvVFCL preinfusion (%)	9.8 ± 4.4	10.5 ± 6.4	8.3 ± 5.8	P = 0.561
cvVFCL postinfusion (%)	8.8 ± 2.8	10.4 ± 5.1	9.0 ± 5.7	P = 0.622
Pre- and postinfusion intragroup cvVFCL <i>t</i> -test	P = 0.575	P = 0.968	P = 0.789	

ANOVA = analysis of variance; VFCL = ventricular fibrillation cycle length; cvVFCL = coefficient of variation ventricular fibrillation cycle length. All data presented as mean ± SD.

myocardium would become less vulnerable to re-excitation due to the reduced number of wavelets. Swartz et al. discovered that human VFCL is determined by the cellular refractory period and not by fibrillation wave front activation.⁶ As such, increasing the VFCL enhances refractoriness and reduces the risk of experiencing sustained VF.

Catecholamine and VFCL

We investigated the impact of a catecholamine infusion designed to mimic the endogenous concentrations achieved during moderate physical or emotional stress on VFCL. We found that catecholamines did not impact the VFCL, suggesting that neither epinephrine nor norepinephrine is likely to promote a further sustaining of VF within the first few seconds after VF initiation. This is in contrast to a study by Suddath et al., which showed that VFCL prolonged to 416 ms at the end of 10 minutes of VF, but returned close to baseline 204 ms ($P < 0.005$) after 1 mg of epinephrine was administered. In that study, VFCL continued to prolong by an additional 16% after the administration of normal saline (placebo) in the control group.¹¹ The time period from VF initiation to administration of

catecholamines and determination of VFCL may explain the differences between our two studies. Tovar and Jones measured VFCL changes occurring from 5 seconds to 5 minutes of VF in isolated rabbit hearts.¹³ VFCL was increased by about 28% over baseline after the first 2 minutes of VF (estimated from the Figure) and by 65% by 5 minutes ($P < 0.001$ at 5 minutes). As such, in our study after only a few seconds of VF, the VFCL is unlikely to be prolonged as it is with longer episodes of VF and the effect of epinephrine may not be apparent.

Beta-Blockers Impact on VFCL

We showed that chronic use of a cardioselective beta-blocker promotes a longer VFCL shortly after VF is initiated. This in addition supports the antifibrillatory benefits of beta-blocker use within a population at high risk of ventricular arrhythmias. As such, the beta-blocking or antiadrenergic effects of sotalol and amiodarone may account, at least in part, for their VFCL increasing effects as well. It is surprising that the VFCL enhancement was evident with or without concurrent catecholamine stimulation suggesting that the effect was likely unrelated to the degree of adrenergic tone.

Table 3. Beta-Blockade Impact on VFCL and cvVFCL

Group	Beta-Blocker (n = 29)	No Beta-Blocker (n = 14)	<i>t</i> -Test
VFCL preinfusion (ms)	194.4 ± 28.8	182 ± 22.4	P = 0.157
VFCL postinfusion (ms)	200.8 ± 26	181.2 ± 4	P = 0.019
cvVFCL preinfusion (%)	8.4 ± 4.8	11.8 ± 6.9	P = 0.216
cvVFCL postinfusion (%)	8.9 ± 4.1	10.5 ± 5.2	P = 0.474

VFCL = ventricular fibrillation cycle length; cvVFCL = coefficient of variation ventricular fibrillation cycle length. All data presented as mean ± SD.

Table 4. VFCL and cvVFCL in Each Group with and without Beta-Blockers

Group	Beta-Blocker (n = 29)			No Beta-Blocker (n = 14)		
	Epinephrine (n = 10)	Norepinephrine (n = 9)	Placebo (n = 10)	Epinephrine (n = 4)	Norepinephrine (n = 5)	Placebo (n = 5)
VFCL preinfusion (ms)	185.1 ± 8.8	202.7 ± 25.5	196.7 ± 30.5	180.3 ± 23.3	179.9 ± 17.6	185.1 ± 9.0
VFCL postinfusion (ms)	193.9 ± 9.1	203.2 ± 17.5	205.2 ± 30.1	183.2 ± 13.2	189.5 ± 20.0	171.7 ± 11.8
cvVFCL preinfusion (%)	9.5 ± 3.8	7.6 ± 3.9	8.0 ± 6.4	10.7 ± 5.9	15.8 ± 10.4	8.8 ± 4.4
cvVFCL postinfusion (%)	8.8 ± 3.3	9.9 ± 3.6	8.0 ± 4.9	8.9 ± 1.6	11.3 ± 7.9	11.1 ± 5.5

VFCL = ventricular fibrillation cycle length; cvVFCL = coefficient of variation ventricular fibrillation cycle length. All data presented as mean ± SD.

VFCL Variability

In a recent study, VFCL variability was demonstrated as a useful predictor of ventricular arrhythmia recurrence.³ Among 26 patients with ICD, followed up to 20 months from the time of electrophysiologic study or ICD implantation, patients with recurrent arrhythmic events had a larger VFCL coefficient of variation (cvVFCL 15.6 vs 9.0, P < 0.001). No differences in mean VFCL occurred between groups. In that study, a cvVFCL ≥ 12 was determined a significant (Hazard ratio 11.7, P = 0.019) predictor for recurrent ventricular arrhythmia among 8 other variables including left ventricular ejection fraction and a QT dispersion of over 80 ms. In another ICD testing study, having a more organized (i.e., more homogeneous) VF waveform was a common component of spontaneous converted arrhythmias versus those VF events that required direct current cardioversion to terminate. This suggests that VF is more prone to terminate spontaneously with lower VFCL heterogeneity.

In our study, infusions of epinephrine and norepinephrine did not significantly alter VFCL variability and the use of beta-blockers did not impact VFCL variability either. This is again in contrast to the study by Suddath et al. where epinephrine reduced VFCL variability, while normal saline allowed a continued increase in VFCL variability. It is probable that the short duration of VF before ICD electrical countershock in our study did not permit elevations in VFCL variability, which could then be corrected by epinephrine, as would occur with 10 minutes of VF, like those in Suddath's study.

LIMITATIONS

This study only investigated the impact of catecholamine infusion and beta-blockers on short-term VF variables. As such, our VFCL and cvVFCL data should not be extrapolated to longer-term VF situations. A well-done previous study suggests that epinephrine would have more dramatic effects on VFCL and cvVFCL, if the period of VF was prolonged as in non-ICD patient cardiac arrest. This previous study utilized chest compressions, which is prudent given the duration of VF used, while our study did not require such compressions since the duration of VF was so short.

We chose doses of epinephrine and norepinephrine designed to achieve blood concentrations similar to that of moderate stress. The impact of markedly higher doses on VFCL or cvVFCL is not known. Although we utilized catecholamines which stimulate beta-1, beta-2, and alpha-1 adrenoceptors, we cannot be sure that other agents which increase cyclic adenosine monophosphate or intracellular calcium do not have an impact on short-term VFCL and VFCL variability.

Since two thirds of our study patients were receiving beta-blockers, the impact of beta-blockers in the non-beta-blocked population with stress levels of catecholamines is not well defined by our study. Epinephrine increased VFCL and decreased cvVFCL in patients with or without beta-blockers. Norepinephrine increased VFCL with or without beta-blockers but the magnitude of increase was greater without beta-blockade. The cvVFCL was increased with norepinephrine and beta-blockers but was decreased among those with norepinephrine but without beta-blockers. If these same subgroup

effects held true in a larger study population, there may have been significant differences between epinephrine and norepinephrine, but this may or may not hold true with larger study populations and this requires further study.

The epinephrine group had a higher incidence of coronary heart disease than the norepinephrine group. The impact of this on overall study results is not known.

CONCLUSION

Moderately dosed epinephrine or norepinephrine does not affect either VFCL or variability of VFCL. Chronic cardioselective beta-blockade prolongs VFCL without any impact on the coefficient of variation of VFCL.

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