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Enhanced Sensitivity to Drug-Induced QT Interval Lengthening in Patients With Heart Failure Due to Left Ventricular Systolic Dysfunction

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Abstract

Patients with heart failure (HF) are at increased risk for drug-induced torsades de pointes (TdP) due to unknown mechanisms. Our objective was to determine if sensitivity to drug-induced QT interval lengthening is enhanced in patients with HF. In this multicenter, prospective study, 15 patients with atrial fibrillation or flutter requiring conversion to sinus rhythm were enrolled: 6 patients with New York Heart Association class II to III HF (mean ejection fraction [EF], 30% $\pm$ 9%), and 9 controls (mean EF, 53% $\pm$ 6%). Patients received ibutilide 1 mg intravenously. Blood samples and 12-lead electrocardiograms were obtained prior to and during 48 hours postinfusion. Serum ibutilide concentrations at 50% maximum effect on Fridericia-corrected QT (QT_F) intervals (EC₅₀) were determined, and areas under the effect (QT_F interval vs time) curves (AUECs) were calculated. Ibutilide concentration–QT_F relationships were best described by a sigmoidal E_{max} model with a hypothetical effect compartment. Median [interquartile range] AUEC from 0 to 4 hours was larger in the HF group than in controls (1.86 [1.86-1.93] vs 1.82 [1.81-1.84] s·h; *P* = .04). Median EC₅₀ was lower in the HF group (0.48 [0.46-0.49] vs 1.85 [1.10-3.23] μ g/L; *P* = .008). Sensitivity to drug-induced QT interval lengthening is enhanced in patients with systolic HF, which may contribute to the increased risk of drug-induced TdP.

Keywords

Arrhythmias; heart failure; pharmacodynamics; QT interval; torsades de pointes

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Torsades de pointes is a potentially life-threatening ventricular arrhythmia that may be induced by inhibitors of the rapid component of the delayed rectifier potassium current (I_{Kr}).¹ More than 50 drugs available in the United States, from multiple classes, may cause torsades de pointes.² Drugs that induce torsades de pointes are used commonly in patients with heart failure. Atrial fibrillation is present in 15% to 30% of patients with heart failure^{3,4} and in as many as 50% of patients with severe heart failure.⁵ Approximately 29% of patients with atrial fibrillation have concomitant heart failure.⁶ Most drugs used for restoration or maintenance of sinus rhythm, including dofetilide, sotalol, ibutilide, and, to a lesser degree, amiodarone and dronedarone, prolong the QT interval and may induce torsades de pointes.²

Patients with heart failure are at increased risk for drug-induced torsades de pointes. In patients with normal left ventricular function, the incidence of dofetilide-induced torsades de pointes is <1%⁷ compared with 3.3% in patients with left ventricular systolic dysfunction.⁸ The incidence of ibutilide-induced torsades de pointes is 1.7% to 4.1% in patients with normal left ventricular function⁹⁻¹¹ but is 5.9% to 11.4% in patients with reduced left ventricular ejection fraction.^{12,13} Heart failure is an independent risk factor for sotalol-induced torsades de pointes.¹⁴ Mechanisms by which heart failure increases the risk of drug-induced torsades de pointes have not been widely studied. Little is known regarding potential variation in relationships between serum concentrations of QT interval-prolonging drugs and QT interval response among populations at risk for drug-induced torsades de pointes.

The purpose of this investigation was to test the hypothesis that patients with heart failure due to left ventricular systolic dysfunction exhibit enhanced sensitivity to drug-induced QT interval lengthening.

METHODS

Study Sites

This study was conducted at 4 academic medical centers: Henry Ford Hospital, an 802-bed tertiary care institution in Detroit, Michigan; Wishard Memorial Hospital, a 353-bed acute care institution; Indiana University Health Methodist Hospital, a 747-bed tertiary care hospital; and the Richard L. Roudebush Veterans Administration Medical Center, a 229-bed hospital, all located in Indianapolis, Indiana.

Patients

Men and women ($n = 15$) >18 years of age with atrial fibrillation or atrial flutter requiring conversion to sinus rhythm were enrolled. Six patients had New York Heart Association (NYHA) class II or III heart failure due to left ventricular dysfunction, determined by medical history, physical examination, and left ventricular ejection fraction between 20% to 40% ascertained by echocardiogram or contrast left ventriculogram. Nine patients comprised a control group with no known history nor current clinical evidence of heart failure, based on physical examination, and/or had documented left ventricular ejection fraction >40%. Exclusion criteria were the following: weight <60 kg; serum potassium <4.0 mEq/L; serum magnesium <1.8 mg/dL; serum hemoglobin <9.0 g/dL; hematocrit <26%; received any Vaughan Williams class IA or III antiarrhythmic agent (except oral amiodarone) within 5 half-lives of ibutilide infusion; baseline Bazett-corrected QT interval >450 milliseconds; history of torsades de pointes; history of sick sinus syndrome; left ventricular ejection fraction <20%; NYHA class IV heart failure; pregnancy; taking any other QT interval-prolonging drugs (except oral amiodarone; QT interval-prolonging drugs were identified based on whether there were any published studies and/or case reports associating the drug with QT interval prolongation or torsades de pointes); permanent pacemaker; and clinical

requirement for a second dose of ibutilide. This study was approved by the Human Rights Committee at Henry Ford Hospital and the Institutional Review Boards at Indiana University–Purdue University–Indianapolis (which reviews protocols to be conducted at Wishard Memorial Hospital and Indiana University Health Methodist Hospital) and the Richard L. Roudebush Veterans Administration Medical Center. All patients provided written informed consent.

Experimental Protocol

One peripheral in-dwelling catheter was inserted into a vein in each arm. Ibutilide 1.0 mg was diluted in normal saline 50 mL and administered intravenously over 10 minutes at a constant rate, controlled by an infusion pump. Ibutilide was selected as the study drug because it substantially increases QT interval and because patients enrolling in this study, who had atrial fibrillation or atrial flutter, could potentially benefit from receiving ibutilide. Ibutilide prolongs the QT interval primarily via inhibition of the rapid component of the delayed rectifier potassium current (I_{Kr}),¹⁵ but activation of a slow inward sodium current may also play a role.¹⁶ Venous blood samples (10 mL) were obtained from the catheter in the contralateral arm from that into which ibutilide was infused and placed into red-top, nonheparinized evacuated collection tubes (Vacutainer, Becton Dickinson, Franklin Lakes, New Jersey). Samples were obtained prior to and at 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours following the end of the ibutilide infusion. Blood samples were immediately placed on ice, allowed to clot, and centrifuged at 2500 rpm for 25 minutes. Serum was harvested and stored at -70°C until analysis. Three 12-lead electrocardiograms (ECGs) were obtained at a paper speed of 25 mm/s, approximately 1 minute apart, at the time of each blood sample. Patients who did not revert to sinus rhythm within 20 to 30 minutes of the end of the ibutilide infusion underwent sedation and direct current cardioversion.

Determination of Serum Ibutilide Concentrations

Serum ibutilide concentrations were determined at the Bioanalytical Core Laboratory, University of Arizona, using reverse-phase high performance liquid chromatography with mass spectrometry detection (Agilent Technology Series 1100 LC/MSD System, Palo Alto, California) equipped with a vacuum degasser, a binary pump, an autosampler, a thermostated column compartment, and a mass selective detector supplied with atmospheric pressure ionization electrospray.¹⁷ Two standard calibration curves were generated, which ranged from 62.5 to 16,000 pg/mL and 15.63 to 1000 pg/mL for samples containing higher and lower ibutilide concentrations, respectively. Intraday and interday coefficients of variation were 7.0%. The lower limit of detection was 15.63 pg/mL; serum concentrations below the lower limit of detection were considered undetectable.

QT Interval Measurements

QT intervals were determined manually by one investigator (H.W.), who was blinded to the patient group, from leads II, V_1 , and V_5 . QT intervals were measured from the earliest QRS deflection to the end of the T wave and included the U wave if it overlapped the T wave. The end of the T wave was defined as the intersection of the terminal portion of the T wave and the isoelectric line. In each measured lead, QT and RR intervals were averaged over 5 consecutive beats to obtain a single mean QT interval from each lead from each ECG. To determine the QT interval at each time point (the time of each blood sample), the mean QT interval from the 3 ECGs at each time point was averaged for each of the 3 measured leads. QT intervals were measured only from ECGs on which the end of the T wave was clearly discernable. QT intervals were corrected using the Fridericia correction (QT_F)¹⁸ to avoid overcorrection associated with the Bazett equation at higher heart rates.¹⁹

Observed Effects on QT_F Interval

Areas under the effect versus time curves (AUECs) for QT_F interval were calculated using the linear trapezoidal rule from 0 to 4 hours (AUEC₀₋₄) and 0 to 8 hours (AUEC₀₋₈) following drug administration. The AUEC was calculated based on observed data and is a model-independent variable.

Pharmacodynamic Modeling of the QT_F Interval—Prolonging Effects of Ibutilide

Pharmacokinetic and pharmacodynamic parameters were estimated using maximum likelihood estimation with ADAPT II, release 4 University of Southern California, Los Angeles, CA.²⁰ The model is described in Supplementary Figure S1 (<http://jcp.sagepub.com/supplemental/>). In addition to these parameters, area under the ibutilide serum concentration versus time curve and ibutilide half-life were determined. The variance equations assumed that the standard deviation of the residuals was linear with increasing serum ibutilide concentrations and QT_F intervals. Model discrimination was accomplished by visual inspection of distribution of the weighted residuals, Akaike information criteria, sums of the squared weighted residuals, and visual predictive checks. The pharmacokinetic model that best fit the serum concentration-time data was a 2-compartment model with first-order elimination from the central compartment. The estimated pharmacokinetic parameters were fixed for each patient for the sequential pharmacodynamic assessment.

Various integrated pharmacokinetic and pharmacodynamic models were assessed to describe ibutilide concentration–QT_F response in the model-building procedure. The final model was selected using the rule of parsimony and the aforementioned model discrimination criteria. Serum ibutilide concentration–QT_F interval relationships were examined in leads II, V₁, and V₅ prior to pharmacodynamic modeling. A subtle delay in ibutilide serum concentrations and QT_F interval lengthening was observed, as manifested by a counterclockwise hysteresis in the concentration–response curves. Therefore, pharmacodynamic models were assessed with and without a theoretical effect compartment to account for the delayed effect. Linear, E_{max}, and sigmoid E_{max} pharmacodynamic models were assessed to describe the ibutilide concentration–response data in (1) each individual lead and (2) the maximum QT_F interval observed in any lead at any given time. The ibutilide concentration–QT_F effect relationships were best described using the maximum QT_F observed from the 3 leads at each sampling time with a sigmoidal E_{max} model with an effect compartment. The effect compartment was required because of the brief delay in the observed response versus serum ibutilide concentrations (Supplementary Figure S1). The following equation describes QT_F interval changes,

$$QT_F = QT_{F_{baseline}} + \frac{E_{max} \cdot [Ce]^\lambda}{EC_{50}^\lambda + [Ce]^\lambda},$$

where E_{max} is the maximum model–derived effect on QT_F, EC₅₀ is the serum ibutilide concentration at which 50% of the maximum QT_F interval effect occurs, Ce is the theoretical serum ibutilide effect compartment concentration, and λ is the Hill coefficient.²¹ The model predicted the QT_F well ($R^2 = .87$) (Supplementary Figure S2).

Sample Size Determination

The intended sample size for this study was 10 patients per group, based on anticipated EC₅₀ of 0.59 and 1.70 μg/L in the heart failure and control groups, respectively, with an expected standard deviation of 0.85 μg/L.

Statistical Analysis

Analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, Illinois). Normality of continuous data was determined using the Kolmogorov-Smirnov test. Statistical comparisons were performed using an unpaired Student *t* test for continuous variables, assuming equal or unequal variances between the groups, or Fisher exact test for categorical variables. For continuous variables that were not normally distributed, the nonparametric Wilcoxon rank-sum test was used. Comparison of the study's pharmacodynamic end points in the 2 groups was performed using the Wilcoxon rank-sum test. For all comparisons, α was set at .05.

RESULTS

Patients

Because of difficulties with patient recruitment, primarily as a result of the numerous exclusion criteria, the final enrolled sample size was 15 patients (heart failure group, $n = 6$; control group, $n = 9$). Patient enrollment was as follows: Henry Ford Hospital ($n = 7$); Wishard Hospital ($n = 6$); Indiana University Health Methodist Hospital ($n = 1$); and Richard A. Roudebush Veterans Administration Medical Center ($n = 1$). Demographic characteristics are presented in Table I. Mean left ventricular ejection fraction in the heart failure group was significantly lower ($30\% \pm 9\%$) than in the control group ($53\% \pm 6\%$, $n = 5$). There were no significant differences in pretreatment QT_F or other demographic characteristics. Of the ECGs used to determine QT_F intervals, 77% were obtained during sinus rhythm.

Observed Effects on QT_F Interval

There was no significant difference between the groups in maximum QT_F following ibutilide administration (Table II). QT interval response data are presented in Figure 1. The mean serum ibutilide concentration versus time curve is presented in Figure 1A; the curves are essentially superimposable, suggesting that any differences observed in QT_F between the groups may not be due to differences in serum ibutilide concentrations. This observation was confirmed in the pharmacokinetic analysis, in which there was no statistically significant difference between the groups in any of the pharmacokinetic parameters. The uncorrected QT interval versus time curve is presented in Figure 1B, and the RR interval versus time curve is presented in Figure 1C. The QT_F versus time (effect) curves in the 2 groups are presented in Figure 1D. The area under the QT_F interval effect versus time curves from 0 to 4 hours ($AUEC_{0-4}$), the time period during which ibutilide-induced torsades de pointes is most likely,²² was significantly larger in the heart failure group (Table II), indicating significantly greater QT_F response. The $AUEC$ from 0 to 8 hours ($AUEC_{0-8}$) was also significantly larger in the heart failure group (Table II, Supplementary Figure S3).

Pharmacodynamic Modeling of the QT_F Interval–Prolonging Effects of Ibutilide

Pharmacodynamic modeling parameters for the effect of ibutilide on QT_F in the heart failure and control groups are presented in Table III. The median EC_{50} in the heart failure group was significantly smaller than that in the control group (Table III, Figure 2). A visual predictive check was performed for the modeling procedure using Monte Carlo simulations ($n = 1000$) of the mean pharmacokinetic and pharmacodynamic parameters. The pharmacodynamic parameters were simulated using the observed variability in heart failure and controls assuming a log-normal distribution. The observed QT_F response versus concentration curves with the median (90th and 10th percentiles) data from the simulations are displayed for heart failure patients and controls in Figures 3A and 3C, respectively. These further demonstrate the predictive performance of the modeling procedure while

displaying the actual patient data. The slightly delayed effect of ibutilide on QT_F lengthening is apparent from observed and simulated QT_F response–concentration curves in the control group. This further demonstrates the need for a model that accounts for this delay, such as the effect compartment model used in this study. The observed QT_F response versus time curves with the median (90th and 10th percentiles) data derived from the simulations for heart failure patients and controls are displayed in Figures 3B and 3D, respectively. There was no significant difference in median E_{max} between the groups.

Adverse Events

Two patients (22.2%) with normal left ventricular function experienced postibutilide arrhythmias compared with none in the heart failure group. One patient developed bigeminy 15 minutes postinfusion, which resolved spontaneously 15 minutes after onset and was not associated with symptoms or hemodynamic instability. In the other patient, junctional tachycardia at a rate of 98 bpm occurred 4 hours postibutilide infusion. Normal sinus rhythm returned spontaneously approximately 2 hours later; the patient experienced no symptoms or hemodynamic instability. No patients in either group developed torsades de pointes.

DISCUSSION

We investigated sensitivity to drug-induced QT lengthening in patients with NYHA class II or III heart failure due to left ventricular systolic dysfunction compared to patients with normal left ventricular function. We found that the median AUEC for QT_F interval was significantly larger in patients with heart failure, indicating greater drug-induced QT_F response. In addition, the median ibutilide EC₅₀ was significantly lower in the heart failure group, indicating greater drug-induced QT_F interval sensitivity in patients with left ventricular dysfunction.

Atrial fibrillation and heart failure commonly coexist. Ibutilide, sotalol, dofetilide, dronedarone, and amiodarone are used in patients with heart failure for management of atrial fibrillation. Many patients with heart failure receive potentially arrhythmogenic antibiotics for a variety of infections; current guidelines recommend fluoroquinolone antibiotics as first-line therapy for community-acquired pneumonia. Approximately 14% of patients with heart failure have major depression, which is associated with increased rates of mortality and hospital readmissions, and increasing numbers of patients with heart failure receive therapy with potentially proarrhythmic antidepressants. Patients with heart failure take many other potentially proarrhythmic drugs as well. Substantial evidence indicates that heart failure increases the risk of drug-induced torsades de pointes.⁷⁻¹⁴

Mechanisms of the increased risk of drug-induced torsades de pointes in patients with heart failure have not been widely studied. The clearance of some drugs is diminished in patients with heart failure because of reduced hepatic blood flow.²³ The volume of distribution of some drugs is decreased in patients with heart failure possibly due to alterations in the extent of drug partitioning into tissues.²³ Therefore, changes in the pharmacokinetics of some drugs, leading to elevated serum concentrations, could be a mechanism of increased risk of drug-induced torsades de pointes in patients with heart failure. However, ibutilide pharmacokinetics are not altered in patients with NYHA class II to III heart failure due to systolic dysfunction,¹⁷ suggesting that changes in serum drug concentrations may not account for the increased risk. In the present study, sensitivity to QT interval lengthening associated with ibutilide was shown to be enhanced in patients with heart failure due to systolic dysfunction.

Mechanisms by which QT interval sensitivity is increased in patients with left ventricular dysfunction are unknown. Downregulation of outward potassium (I_{Kr}, I_{to})²⁴⁻²⁶ and inward

rectifying currents (I_{K1})²⁷ and upregulation of inward calcium and/or late sodium currents^{26,28,29} have been demonstrated in heart failure, which may convey increased QT interval sensitivity. Development and progression of heart failure lead to prolongation in ventricular repolarization.³⁰ Dispersion of ventricular repolarization has been demonstrated in failing hearts.³¹ Further, transmural dispersion in myocardial contractility is present in symptomatic long QT interval mutation carriers, which may be related to the risk of spontaneous torsades de pointes.³² The contribution of these and other as yet undetermined mechanisms to enhanced sensitivity to drug-induced QT interval lengthening and facilitation of torsades de pointes requires further study.

Few published data exist regarding the effects of repolarization-prolonging drugs in patients with left ventricular systolic dysfunction. Cheng et al³³ investigated the effects of ibutilide on temporal variability in ventricular repolarization in patients with left ventricular systolic dysfunction (n = 13) and in patients with normal left ventricular function (n = 8), who were referred for electrophysiology study for sudden cardiac death risk stratification or radiofrequency ablation of supraventricular tachycardia. Ibutilide provoked significant QT interval and monophasic action potential duration prolongation in both the heart failure group and the control group; however, direct comparisons of the effects of ibutilide on QT interval and monophasic action potential duration in the heart failure group versus control group were not provided. Our study builds on Cheng et al's findings by (1) relating changes in QT interval lengthening to serum ibutilide concentrations and (2) providing a direct comparison of the effects of ibutilide on ventricular repolarization in patients with left ventricular systolic dysfunction compared to those with normal left ventricular function. Our study is the first to report enhancement in sensitivity to drug-induced QT interval lengthening in patients with heart failure due to left ventricular systolic dysfunction.

In the present study, the effect of ibutilide on observed maximum QT_F was not significantly different in the 2 groups. In addition, serum ibutilide concentrations in the 2 groups were not different. Therefore, the greater effect of ibutilide on the AUEC of the QT_F in the heart failure group compared to that in the control group and the markedly lower ibutilide EC₅₀ in the heart failure group represent a sustained effect of ibutilide-induced QT_F interval lengthening and indicate a period of prolonged proarrhythmic risk in the heart failure group. Mechanisms underlying this sustained effect of ibutilide on QT_F intervals in patients with left ventricular systolic dysfunction require further study.

Limitations of this study include the relatively small sample size. However, despite the sample size, we demonstrated significant differences in AUEC and EC₅₀. In addition, 23% of the QT_F measurements in the study were made while patients were in atrial fibrillation. Measurement and correction of QT intervals during atrial fibrillation are more difficult than during sinus rhythm.³⁴ However, because of the potential risks, we could not ethically administer ibutilide at therapeutic doses to heart failure volunteers in sinus rhythm. In addition, when the study was initiated, the sensitivity of available serum ibutilide concentration assays was limited, so that administration of small doses of ibutilide to heart failure volunteers would not have allowed detectable serum ibutilide concentrations for calculation of EC₅₀. Therefore, the study was designed to administer ibutilide to patients with atrial fibrillation or flutter who could potentially benefit from the drug. Despite the issues with QT interval measurement and correction in atrial fibrillation, the majority of our ECGs were obtained while patients were in sinus rhythm. The majority of the ECGs obtained during atrial fibrillation were baseline, preibutilide ECGs. We excluded ECGs from analysis, whether from patients in atrial fibrillation or sinus rhythm, if the T wave was not clearly discernible. Another limitation is that we tested only one QT interval-prolonging drug, ibutilide, which inhibits I_{Kr} and activates slow inward sodium current.^{15,16} Our results require confirmation with additional QT interval-prolonging drugs.

In conclusion, patients with NYHA class II or III heart failure due to left ventricular systolic dysfunction exhibit enhanced sensitivity to drug-induced QT interval lengthening, which may contribute to the increased risk of drug-induced torsades de pointes in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

(A) Serum ibutilide concentrations versus time in patients with heart failure due to left ventricular systolic dysfunction and in a control group of patients with normal left ventricular function. (B) Uncorrected QT intervals versus time in patients with heart failure due to left ventricular systolic dysfunction and in a control group of patients with normal left ventricular function. (C) RR intervals versus time in patients with heart failure due to left ventricular systolic dysfunction and in a control group of patients with normal left ventricular function. (D) QT_c intervals versus time in patients with heart failure due to left ventricular systolic dysfunction and in a control group of patients with normal left ventricular function. All values are mean $\pm$ standard deviation.

Figure 2.

EC₅₀ in patients with heart failure and in the control group. EC₅₀ = serum ibutilide concentration at which 50% maximum effect on QT_F intervals occurred. Box plots indicate median EC₅₀. Upper and bottom portions of the box are 75th and 25th percentiles, respectively. Upper and lower bars represent maximum and minimum values, respectively.

Figure 3.

(A) Relationship between QT_F and serum ibutilide concentrations in the heart failure group (○). Visual predictive checks are displayed, with the solid line representing the 50th percentile and the dashed lines representing the 90th and 10th percentiles generated from Monte Carlo simulations ($n = 1000$) using the mean pharmacodynamic parameters and variability and mean pharmacokinetic parameters from the modeling procedure. The solid vertical line represents the model-predicted EC₅₀ for heart failure patients. (B) Maximum QT_F versus time in the heart failure group (○). The solid line represents the 50th percentile, and the dashed lines represent the 90th and 10th percentiles from the visual predictive checks. (C) Relationship between QT_F and serum ibutilide concentrations in the control group (•). Visual predictive checks are displayed, with the solid line representing the 50th percentile and the dashed lines representing the 90th and 10th percentiles generated from Monte Carlo simulations ($n = 1000$) using the mean pharmacodynamic parameters and variability and mean pharmacokinetic parameters from the modeling procedure. The solid vertical line represents the model-predicted EC₅₀ for the control group. (D) Maximum QT_F versus time in the control group (•). The solid line represents the 50th percentile, and the dashed lines represent the 90th and 10th percentiles from the visual predictive checks.

Table I

Characteristics of Patients

Characteristic	Heart Failure (n = 6)	Normal LV Function (n = 9)	P
Age, y	53 ± 17	60 ± 20	.50
Female sex, n (%)	3 (50)	1 (11)	.24
African American race, n (%)	5 (83)	4 (44)	.51
Weight, kg	105 ± 37	80 ± 31	.35
LVEF, %	30 ± 9	53 ± 6 (n = 5)	.0001
Hypertension, n (%)	3 (50)	5 (56)	>.99
Diabetes mellitus, n (%)	2 (33)	2 (22)	.58
Coronary artery disease, ^a n (%)	0	1 (11)	>.99
Past MI, n (%)	1 (17)	2 (22)	>.99
COPD, n (%)	0	1 (11)	>.99
Pretreatment serum K ⁺ , mEq/L	4.3 ± 0.2	4.3 ± 0.2	.78
ACEI/ARB, n (%)	3 (50)	3 (33)	.62
β-blockers, n (%)	4 (67)	4 (44)	.61
Diuretics, n (%)	3 (50)	4 (44)	>.99
Nitrates, n (%)	3 (50)	3 (33)	.62
Oral amiodarone, n (%)	1 (17)	1 (11)	>.99
Ibutilide-induced conversion to SR, n (%)	2 (33)	5 (56)	.61
DCC-induced conversion to SR, n (%)	2 (33)	4 (44)	.61
Pretreatment QT _F , milliseconds	419 ± 20	410 ± 34	.95

Data are mean ± standard deviation unless otherwise indicated. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; DCC, direct current cardioversion; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; QT_F, Fridericia-corrected QT interval; SR, sinus rhythm.

^aNo history of MI.

Table II

Observed QT Interval Response Associated With Ibutilide in Patients With Heart Failure and in Patients With Normal Left Ventricular Function

Parameter	Heart Failure (n = 6)	Normal Left Ventricular Function (n = 9)	P
Maximum QT _F (leads II, V ₁ , V ₅), s	0.491 (0.482-0.522)	0.495 (0.481-0.527)	.95
Maximum QT _F (lead II), s	0.485 (0.474-0.494)	0.490 (0.481-0.506)	.44
Maximum change in QT _F from pretreatment value (leads II, V ₁ , V ₅), %	17 (17-18)	21 (13-29)	.78
AUEC ₀₋₄ , s·h	1.86 (1.86-1.93)	1.82 (1.81-1.84)	.04
AUEC ₀₋₈ , s·h	3.67 (3.62-3.79)	3.56 (3.52-3.60)	.04

Data are presented as median (interquartile range). AUEC, area under the effect curve for QT_F interval versus time; QT_F, Fridericia-corrected QT interval.

Table III

Pharmacodynamic Modeling Parameters for Effect of Ibutilide on QT Intervals in Patients With Heart Failure and in Patients With Normal Left Ventricular Function

Parameter	Heart Failure (n = 6)	Normal Left Ventricular Function (n = 9)	P
EC ₅₀ , µg/L	0.48 (0.46-0.49)	1.85 (1.10-3.23)	.008
E _{max} , s	0.491 (0.475-0.519)	0.545 (0.517-0.576)	.07
Hill coefficient (λ)	3.21 (1.52-7.16)	0.75 (0.58-3.67)	.22
Keo, h ⁻¹	0.20 (0.10-7.20)	0.04 (0.02-0.07)	.05

Data presented as median (interquartile range). EC₅₀, serum ibutilide concentration at which 50% of the maximum QT_F interval effect occurs. E_{max}, maximum model-derived effect on QT_F interval. Keo, equilibrium rate constant from the central compartment to the theoretical effect compartment.