Basic Science and Experimental Studies

Vernakalant in an Experimental Model of Pacing-Induced Heart Failure: Lack of Proarrhythmia Despite Prolongation of Repolarization

GERRIT FROMMEYER, MD,[1] JOCHEN SCHULZE GROTTHOFF, MS,[1] CHRISTINA FISCHER, MS,[1] HARILAOS BOGOSSIAN, MD,[2] FLORIAN REINKE, MD,[1] SIMON KOCHHÄUSER, MD,[1] DIRK G. DECHERING, MD,[1] MICHAEL FEHR, PhD,[3] PETER MILBERG, MD,[1] AND LARS ECKARDT, MD[1]

Münster, Witten-Herdecke and Hanover, Germany

ABSTRACT

Background: The present ESC guidelines on atrial fibrillation have introduced vernakalant (VER) for pharmacologic cardioversion of atrial fibrillation. The aim of the present study was to investigate possible proarrhythmic effects of vernakalant in an experimental model of heart failure (HF).

Methods and Results: In 12 female rabbits, HF was induced with the use of 4 weeks of rapid ventricular pacing. Twelve rabbits were sham operated. Isolated hearts demonstrated a significant prolongation of myocardial repolarization after induction of HF. Vernakalant caused a concentration-dependent (10 μmol/L and 30 μmol/L) increase of action potential duration (APD_{90}) and QT interval without affecting spatial and temporal dispersion of repolarization. The increase in APD_{90} was accompanied by a greater increase in refractory period resulting in a significant increase in post-repolarization refractoriness. In control conditions, programmed ventricular stimulation and burst pacing led to ventricular fibrillation (VF) in 2 of the 12 sham (4 episodes) and in 3 of the 12 HF (24 episodes) subjects. In the presence of 30 μmol/L vernakalant, VF was no longer inducible in both groups (0 episodes). In the presence of low K^+ concentration, neither sham nor HF vernakalant-treated subjects developed early after-depolarizations or ventricular tachyarrhythmias.

Conclusion: In the present study, application of vernakalant led to a significant prolongation of myocardial repolarization and increased post-repolarization refractoriness but did not induce early after-depolarization and therefore did not cause proarrhythmia in failing hearts. (*J Cardiac Fail 2014;20:786–792*)

Key Words: Vernakalant, heart failure, dispersion of repolarization, polymorphic ventricular tachycardia, proarrhythmia.

Vernakalant has recently been introduced for rapid pharmacologic conversion of recent-onset atrial fibrillation (AF) in patients without severe structural heart disease.[1,2] In several randomized clinical studies, a beneficial effect of vernakalant compared with placebo[3,4] or other antiarrhythmic drugs, such as amiodarone,[5] was reported. In a small prospective single-center study, superiority to flecainide in conversion rate and conversion time was demonstrated.[6] Vernakalant was therefore included in the 2012 focused update of the European Society of Cardiology (ESC) guidelines for management of AF and received a class 1A recommendation for pharmacologic conversion of recent-onset AF in patients without severe structural heart disease.[7] In a meta-analysis, in which data from

From the [1]Division of Electrophysiology, Department of Cardiovascular Medicine, University of Münster, Münster, Germany; [2]Märkische Kliniken, Department of Cardiology and Angiology, Klinikum Lüdenscheid, University of Witten-Herdecke, Witten-Herdecke, Germany and [3]Clinic of Exotic Pets, Reptiles, and Exotic and Feral Birds, University of Hanover, Hanover, Germany.

Manuscript received March 26, 2014; revised manuscript received June 27, 2014; revised manuscript accepted July 23, 2014.

Reprint requests: Dr med Gerrit Frommeyer, MD, Abteilung für Rhythmologie, Department für Kardiologie und Angiologie, Universitätsklinikum Münster, Albert-Schweitzer Campus 1, D-48149 Münster. Tel: (+49) 251-834 8370; Fax: (+49) 251-834 9965. E-mail: gerrit.frommeyer@ukmuenster.de

Funding: Dr Peter Osypka Foundation. Lars Eckardt holds the Peter Osypka Professorship for Experimental and Clinical Electrophysiology.

See page 792 for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2014.07.013

patients with ischemic heart disease or previous cardiac surgery were extracted, no negative effect of vernakalant was reported.[8] In fact, in that study population, which included patients up to New York Heart Association (NYHA) functional class III, a significant success rate in conversion of AF was observed.[8] Those results were confirmed by Kowey et al,[9] who also reported a beneficial effect in patients after cardiac surgery. Nonetheless, vernakalant is contraindicated in patients with relevant structural heart disease or severe clinical heart failure (HF) as well as in patients with a history of pharmacologic QT prolongation or torsades de pointes.

The antiarrhythmic effect of vernakalant is based on a mixed block of cardiac K^+ and Na^+ channels and thereby exerts multiple effects on cardiac repolarization. Studies in atrial sleeve preparations have proven a rather atrial-selective effect of vernakalant,[10] which is mainly related to the late Na^+ channel ($I_{Na,late}$).[11] Inhibition of $I_{Na,late}$ seems to be a promising therapeutic approach for pharmacotherapy of AF, because the $I_{Na,late}$ inhibitor ranolazine has proven to be effective in reduction of AF in experimental[12,13] and clinical[14] studies. Of note, $I_{Na,late}$ inhibitors have been successfully used in models of HF.[15,16]

Whether the electrophysiologic effects of vernakalant, including QT prolongation, may trigger proarrhythmia in the setting of a reduced repolarization reserve[17] induced by HF has not yet been investigated. Therefore, the aim of the present study was to examine a possible proarrhythmic potential of vernakalant in a sensitive whole-heart model of proarrythmia[16,18,19] in HF where myocardial repolarization is already altered, compared with structural normal hearts.[18]

Methods

All experimental protocols were approved by the local animal care committee and conformed to the "Guide for the Care and Use of Laboratory Animals" published by the USA National Institutes of Health (NIH publication no. 852-3, revised 1996).

Induction of Heart Failure

HF was induced by continuous rapid ventricular pacing (400 beats/min) for 3−4 weeks. The method has recently been described in detail by our group.[18] Twelve adult female New Zealand white rabbits weighing 3.5−4.0 kg were anesthetized with the use of ketamine (75 mg/kg) and xylazine (5.8 mg/kg), with additional doses administered as needed. A pacemaker lead was implanted into the right ventricle via the right jugular vein under fluoroscopic guidance. One week after the operation, an external pacemaker was connected and rapid pacing was started. Over a period of 3−4 weeks, the rabbits were monitored by clinical examination and echocardiography to determine whether they developed HF. For performance of echocardiography, the rabbits were anaesthetized with isoflurane. Sham-operated rabbits (n = 12) received a right ventricular pacing lead but were not paced and were used as control subjects.

Preparation of Hearts for Perfusion

The method of preparing the hearts has been previously described in detail.[19] Rabbits were anaesthetized with the use of sodium thiopental (200−300 mg intravenously). After midsternal incision and opening of the pericardium, the complete hearts were removed and immediately placed in an ice-cold Krebs-Henseleit solution (composition in mmol/L: $CaCl_2$ 1.80, KCl 4.70, KH_2PO_4 1.18, $MgSO_4$ 0.83, NaCl 118, $NaHCO_3$ 24.88, Na-pyruvate 2.0, and D-glucose 5.55). The aorta was cannulated, the pulmonary artery was incised, and the spontaneously beating hearts were perfused at constant flow (52 mL/min) with warm (36.8°C−37.2°C) Krebs-Henseleit solution. Perfusion pressure was continuously measured during the experiments and stayed stable at ∼100 mm Hg. The hearts were placed in a heated solution-filled tissue bath. The perfusate was equilibrated with 95% O_2 and 5% CO_2 (pH 7.35, 37°C). The cannulated and perfused hearts were attached to a vertical Langendorff apparatus (Hugo Sachs Electronic, Medical Research Instrumentation, March-Hugstetten, Germany).

Electrocardiographic and Electrophysiologic Measurements

Signals from a simulated "Einthoven" configuration were amplified by a standard electrocardiographic (ECG) amplifier (filter settings 0.1−300 Hz), and QT interval was measured. Monophasic action potential (MAP) recordings and stimulation were accomplished simultaneously with the use of contact MAP pacing catheters (EP Technologies, Mountain View, California). The MAP electrograms were amplified and filtered (low pass 0.1 Hz, high pass 300 Hz). MAPs were analyzed with the use of specifically designed software permitting precise definition of the amplitude and duration of the digitized signals. The recordings were considered to be reproducible and therefore acceptable for analysis only if they had stable baseline amplitude with a variation of $<$20% and a stable duration measured at 90% repolarization (90% action potential duration [APD_{90}]). Seven MAPs were evenly spread in a circular pattern around both ventricles; 1 MAP was recorded from the left ventricular endocardium. Pacing at 2 times the diastolic threshold was performed for 1 minute at each cycle length (CL) from 900 ms to 300 ms (Universal Programmable Stimulator, UHS 20, Biotronik, Germany). All data were digitized at a rate of 1 kHz with 12-bit resolution and subsequently stored on a removable hard disk (Bard Lab System, Bard Electrophysiology, Murray Hill, Massachusetts).

Protocols for Ex Vivo Experiments

Cycle length dependence of MAP duration was investigated under baseline conditions by pacing the hearts at CLs from 900 ms to 300 ms. Subsequently, programmed stimulation was performed with up to 2 external stimuli to determine the effective refractory period (ERP). A premature stimulus (S2) was introduced after each train of 8 basic beats. Coupling interval was reduced gradually until failure to capture occurred, defining ERP. The coupling interval was initially set late in diastole and subsequently reduced by 10 ms until no capture was observed. The coupling interval was then increased by 10 ms and then decreased by 2 ms until capture was lost. After determination of S2, the coupling interval was increased by 20 ms to reach a safe capture and a second external stimulus was introduced for determination of S3. Subsequently, S3 was defined in the same way as S2. In case of induction of ventricular fibrillation (VF), the hearts were defibrillated, followed by