Hemodynamic Effects of Late Sodium Current Inhibitors in a Swine Model of Heart Failure

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ABSTRACT

Objectives: To evaluate possible treatment-related hemodynamic changes, we administered ranolazine or mexiletine to swine with heart failure (HF) and to controls.

Background: Ranolazine and mexiletine potently inhibit depolarizing late Na^+ current ($I_{Na,late}$) and Na^+ entry into cardiomyocytes. Blocking Na^+ entry may increase forward-mode Na/Ca exchange and reduce cellular Ca^{+2} load, further compromising systolic contraction during HF.

Methods and Results: Anesthetized tachypaced HF swine received ranolazine (n = 9) or mexiletine (n = 7) as boluses, then as infusions; the same experiments were performed in 10 nonpaced controls. The swine with HF had characteristic elevated left ventricular end-diastolic pressure (LVEDP) and reduced maximal left ventricular pressure rise ($+dP/dt_{max}$) and left ventricular peak systolic pressure (LVSP). No significant change occurred after ranolazine dosing for any parameter: LVEDP, $+dP/dt_{max}$, LVSP, heart rate, maximal LV pressure fall rate ($-dP/dt_{max}$), or time constant for isovolumic relaxation. Similar results seen in additional swine with HF: 7 were given mexiletine, and 7 others were given ranolazine after a 27% rate decrement to maximize $I_{Na,late}$. Patch-clamped HF cardiomyocytes confirmed drug-induced $I_{Na,late}$ blockade.

Conclusions: Ranolazine or mexiletine blocking $I_{Na,late}$ neither worsened nor improved hemodynamics during advanced HF. Although results must be clinically confirmed, they suggest inhibition of $I_{Na,late}$ by ranolazine or mexiletine may not exacerbate HF in patients. (*J Cardiac Fail 2019;25:828–836*)

Key Words: Ranolazine, mexiletine, systolic dysfunction, action potential.

Introduction

Ranolazine, a potent and specific inhibitor of late sodium current ($I_{Na,late}$), is commonly used to treat angina pectoris or to suppress arrhythmia.[1-4] Mexiletine, also a potent inhibitor of $I_{Na,late}$, is approved to suppress arrhythmia.[5,6] Some patients receiving these drugs are likely to have heart failure (HF) due to ischemia or other causes of myocardial mechanical dysfunction. The consequences of $I_{Na,late}$ inhibition have not been studied in patients with advanced Mattiello JA, Margulies KB, Jeevanandam V, Houser SR. Contribution of reverse-mode sodium-calcium exchange to contractions in failing human left ventricular myocytes. Cardiovasc Res 1998; 37:424–431. Mattiello JA, Margulies KB, Jeevanandam V, Houser SR. Contri- . Ranolazine, a potent inhibitor of $I_{Na,late}$, is commonly used to treat angina pectoris and suppress arrhythmia.[1–5] Mexiletine, also a potent inhibitor of $I_{Na,late}$, is approved to suppress arrhythmia.[6,7] Certain patients receiving these drugs are likely to have HF due to ischemia or other causes of myocardial mechanical dysfunction. The consequences of $I_{Na,late}$ inhibition for hemodynamic performance have not been studied in patients with HF, although this ionic current is significantly increased in failing cardiomyocytes. Such increases in $I_{Na,late}$ likely figure in the prolonged action potential duration (APD) often observed during advanced HF[8] as well as HF-associated instability of repolarization, early and delayed after-depolarization and re-entrant arrhythmia.[9,10] By shortening the plateau phase of the action potential and reducing a depolarizing current, drug-induced inhibition of

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$I_{Na,late}$ may suppress early after-depolarization and thereby prevent certain HF-related arrhythmias,[11] particularly when repolarization is delayed,[12] a characteristic feature of HF. The recently completed RAID (Ranolazine Implantable Cardioverter-Defibrillator) trial found that ranolazine was effective in preventing recurrent implantable cardiac defibrillator therapies for ventricular tachycardia, and one would anticipate increased use of ranolazine as an antiarrhythmic drug.[13] The influence of $I_{Na,late}$ inhibition on contractile performance appears to be more complex. Because Na^+ entry is increased, the Na^+-Ca^{+2} exchanger, enhanced in HF,[14–16] will raise Ca^{+2} entry into failing cardiomyocytes, favoring greater Ca^{+2} stores in the sarcoplasmic reticulum and more intense contraction during systolic Ca^{+2} release.[17] This may provide a significant source of mechanical support for the failing cardiomyocyte.[18] Drug-induced inhibition of $I_{Na,late}$ could diminish Na entry, reduce sarcoplasmic Ca^{+2} release, and possibly worsen systolic dysfunction in patients with advanced HF. Indeed, using a recognized model of myocyte ionic function,[19] we confirmed the possibility of significantly reduced Ca^{+2} release and diminished Ca^{+2} stores when augmented $I_{Na,late}$ modeling HF was inhibited. At the same time, we hypothesized that drug-induced inhibition of $I_{Na,late}$ and diminished Na^+-Ca^{+2} exchange may reduce myoplasmic Ca^{+2} overload, relaxing the excessive diastolic tension associated with HF.[20] To clarify the net hemodynamic consequences of ranolazine or mexiletine administration during advanced HF, we studied the actions of these drugs when administered intravenously to a closed-chest swine model of HF. We also exposed cardiomyocytes from the failing swine left ventricle to levels of ranolazine or mexiletine achieved in vivo to assess drug influence on cellular electrophysiologic function.

Methods

Tachycardic Pacing Model of Heart Failure

Induction of HF was carried out as described previously[21] using protocols approved by the Uniformed Services University Institutional Animal Care and Use Committee in accordance with all applicable federal regulations governing the protection of animals in research. In summary, Yorkshire swine (15−30 kg) of either sex were implanted in the right ventricle with a St. Jude Medical pacing lead under fluoroscopic observation and paced at 200 beats per minute. The progression of systolic dysfunction was monitored weekly during rapid pacing by serial echocardiography until left ventricular (LV) fractional shortening, when pacing was paused, fell to < 16%, usually in 3 to 5 weeks. For the 23 animals with HF used in this investigation, the mean shortening fraction was 11.6% ± 2.6% (SD) 1 day prior to acute study. Tachypacing was halted 2 hours prior to sedation, instrumentation and drug administration.

Left Ventricular Pressure Recording and Intravenous Drug Administration

Swine (HF or nonpaced controls) were sedated with sodium pentobarbital or propofol and ventilated via tracheal intubation. A Millar pressure catheter (model SPR-550-5) was advanced from the right carotid artery into the LV cavity. Arterial and LV pressures and heart rate were monitored by a Millar MPVS Ultra interface and LabChart software. LV pressure parameters—maximum, minimum, and end-diastolic pressure, $\pm dP/dt_{max}$, and time constant (τ) of ventricular relaxation—were averaged for 25 successive beats. Electrocardiogram was recorded from surface electrodes.

Animals with HF were allocated in random order to receive either ranolazine or mexilitene without regard to hemodynamic values or other characteristics. Similar nonpaced control swine were also randomized to these treatments to determine whether full doses of ranolazine or mexiletine affected their hemodynamics.

Ranolazine or mexiletine was administered via jugular catheter as bolus injections followed by 10−20-minute infusions (Fig. 1). Ranolazine in saline (pH 4.0), given as increasing bolus doses of 0.25, 1.25 and 2.25 mg/kg at 10-minute intervals, was followed by a constant infusion of

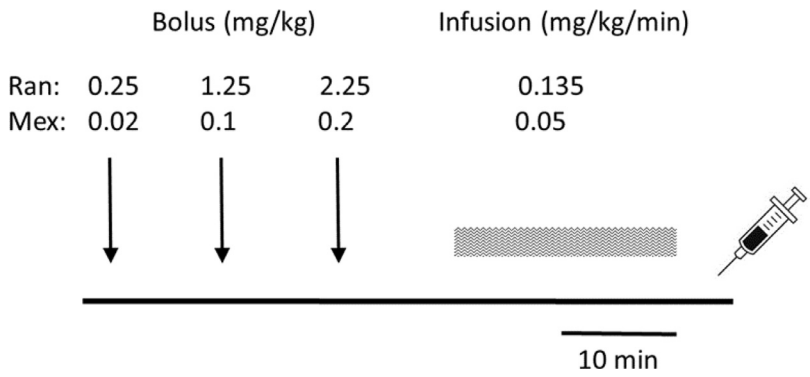

Fig. 1. Experimental protocol. Swine were anesthetized and instrumented, as described, before starting drug administration. Hemodynamic performance and ECG were recorded continuously. Beginning soon after predrug baseline measurements, swine were given 3 successive boluses of ranolazine (Ran) or mexiletine (Mex) at arrows, using escalating doses with 10 minutes interposed to allow drug distribution. Swine then received infusions (shading) of the same drug at the doses indicated. Upon completion, hemodynamic values were recorded, blood samples were obtained for drug levels, and the in vivo phase was terminated, with harvest of tissues for in vitro studies.

0.135 mg/kg/min for 20 minutes. Mexiletine in saline (pH 7.4) was administered as bolus doses of 0.02, 0.1 and 0.2 mg/kg followed by a 0.05 mg/kg/min infusion. In randomly selected experiments using 7 previously untreated HF swine, ivabradine in saline was injected as 0.3 mg/kg boluses with additional 0.1 mg/kg as needed to lower heart rate to 70 beats per minute prior to administration of ranolazine as just described. This was done before baseline hemodynamic measurements to test ranolazine in animals with HF when $I_{Na,\ late}$ was maximized by the slow heart rate.[22] Blood samples taken just after completed dosing of ranolazine or mexiletine were assayed for plasma concentration by high-performance liquid chromatography. Animal test groupings (HF/control): 9/6 ranolazine, 7/4 mexiletine, and 7 HF ranolazine plus ivabradine. All animals were euthanized at the end of the drug administration protocol, and cardiac tissue was obtained for in vitro study.

Assessment of Cardiomyocyte Electrophysiology

Myocytes were isolated from anterior LV as described previously[21] approximately 3 hours after completion of hemodynamic studies. Ionic currents under whole-cell patch (voltage)-clamp were recorded using an Axon Instruments Axopatch 200-B amplifier (CV203 headstage) coupled to a Digdata 1440A interface and controlled by PClamp 10 software. Thick-walled microelectrodes were fire-polished and coated close to the tip with Sylgard (1-3 MΩ).

For measurements of the early Na^+ current amplitude, bathing and pipette solutions were designed to suppress contaminating ionic current and transporters by use of ion substitution, pharmacologic blockers and an adenosine triphosphate (ATP)-regenerating system. The extracellular solution was made up of the following mM concentrations: NaCl 130, CsCl 10, Na HEPES 10, $MgCl_2$ 2.6, $CaCl_2$ 0.1, and glucose 5, with pH 7.4. The pipette solution contained the following mM concentrations: Cs aspartate 120, TEA Cl 20, H^+ HEPES 10, ATP 5, $MgCl_2$ 5.36, Na_2 creatine phosphate 5, EGTA 1, $CaCl_2$ 0.34, and pH 7.2. Concentrations of free Ca^{+2} and Mg^{+2}, calculated from MaxChelator, were 0.1 μM and 1 mM, respectively. Ranolazine was dissolved in DMSO and diluted to the desired final concentration. Mexiletine was prepared as stock solutions in an extracellular solution, then diluted to the desired concentration. Na^+ currents were recorded after electronic compensation of series resistance (70%−90%) and capacitance. Holding potential was −120 mV.

Action potentials were measured in control and HF myocytes under current clamp conditions. The extracellular solution contained (mM) NaCl 140, KCl 5.4, HEPES 10, $CaCl_2$ 1.8, $MgCl_2$ 1, glucose 10, pH 7.4, temp 32C−36C. The pipette solution contained K aspartate 140, HEPES 10, ATP 5, total Mg 5.4 (free Mg^{+2} 1 mM), Na_2 creatine phosphate 5, EGTA 0.1, $CaCl_2$ 0.03 (free Ca^{+2} 100 nM) with a pH of 7.2.

Statistics

Each hemodynamic value was measured using a LabChart algorithm, which quantified and averaged measurements during 25 successive cardiac cycles. The resultant average was recorded as the value of a specific parameter for a given animal at start or end of the drug-administration protocol. Group means and variances were calculated using each recorded average value as a single data point.

Based on earlier results,[21] we hypothesized that previously tachypaced animals would have hemodynamic alterations at predrug baseline indicative of HF when compared to baselines in nonpaced controls. To test this hypothesis, we compared grouped mean predrug baseline values of HF and control animals using an unpaired Student t test, with $P < 0.05$ deemed significant. Analysis of variance demonstrated baseline homogeneity in all animals with HF and in all control animals, regardless of later drug treatment. Hence, all swine with HF and all control swine were pooled for this comparison. Predrug baseline measurements were single values obtained from each animal just prior to initiation of drug treatment.

We further hypothesized that each animal would exhibit maximal ranolazine or mexiletine effect at peak treatment, that is, the time of completion of drug administration (boluses and subsequent infusion). Drug effects were evaluated independently in animals with HF and in controls to determine whether there were unique drug actions in either group. We utilized a paired comparison, relating the value in each animal at peak treatment to pretreatment baseline in the same animal. For our null hypothesis, we postulated that treatment groups, on average, would show no difference between hemodynamic values at predrug baseline and at peak treatment, as just defined. To satisfy this null hypothesis for each parameter, the mean difference on paired comparison between baseline and peak would not differ from 0, that is, the 95% uncertainty limits associated with each mean difference would include 0.

Results

Heart Rate and Left Ventricular Pressure Parameters in Controls and Swine With Heart Failure

Control animals (n = 10) had slightly raised mean baseline heart rates and left ventricular end-diastolic pressures (LVEDP) relative to published values for unanesthetized swine, likely effects of anesthesia and mechanical ventilation. Compared with controls, previously tachypaced swine (n = 23) at baseline had markedly elevated LVEDP, decreased left ventricular peak systolic pressure (LVSP) and diminished $+dP/dt_{max}$ and $-dP/dt_{max}$ plus prolonged systolic relaxation times (τ), each characteristic features of advanced HF (Table 1).

Effects of Ranolazine Adminstration

All animals receiving ranolazine remained in sinus rhythm without consistent change in ECG parameters during the

Table 1. Pretreatment Mean (± SD) Baseline Heart Rate and Left Ventricular Pressure Parameters in Anesthetized Swine: Control vs Heart Failure

	N	HR	LVSP	LVEDP	$+dP/dt_{max}$	$-dP/dt_{max}$	τ
Control	10	114 ± 14	116 ± 16	18 ± 4	2314 ± 299	−3261 ± 607	0.032 ± .0062
HF	23	108 ± 26	98* ± 19	28* ± 11	1269* ± 502	−1356* ± 687	0.141* ± .082

$+dP/dt_{max}$, maximum rate of LV pressure rise (mmHg/sec); $-dP/dt_{max}$, maximum rate of LV pressure fall (mmHg/sec); HF, heart failure; HR, heart rate (beats/min); LV, left ventricle; LVSP, peak LV systolic pressure (mmHg); N, number of animals; τ, time constant for isovolumic LV relaxation (sec).

*$P \leq 0.01$ vs controls.

Note: All animals in each drug study group were included in this table, arranged according to the presence (HF) or absence (control) of prior tachypacing. Each animal had a single study and contributed a single value, measured just prior to ranolazine, mexiletine or ivabradine.

course of the study. Ranolazine plasma concentrations at the end of the infusion period were 6.3 ± 1.7 μg/mL (SEM), equivalent to 13.6 ± 3.8 μM (n = 11). Contributing plasma values from animals with and wihout HF were pooled in these calculations because the means for ranolazine were not statistically different. For either controls or animals with HF, bolus injections of ranolazine resulted in a transient, dose-dependent reduction of LVSP and $+dP/dt_{max}$ but no consistent change in other measured parameters (Fig. 2). Paired comparisons between measurement at pretreatment baseline and maximal treatment at completion of infusion showed no detectable change in heart rate or any LV pressure parameter for controls (n = 6) or for animals with HF (n = 9) (Table 2A). In each case for swine with HF, the mean change

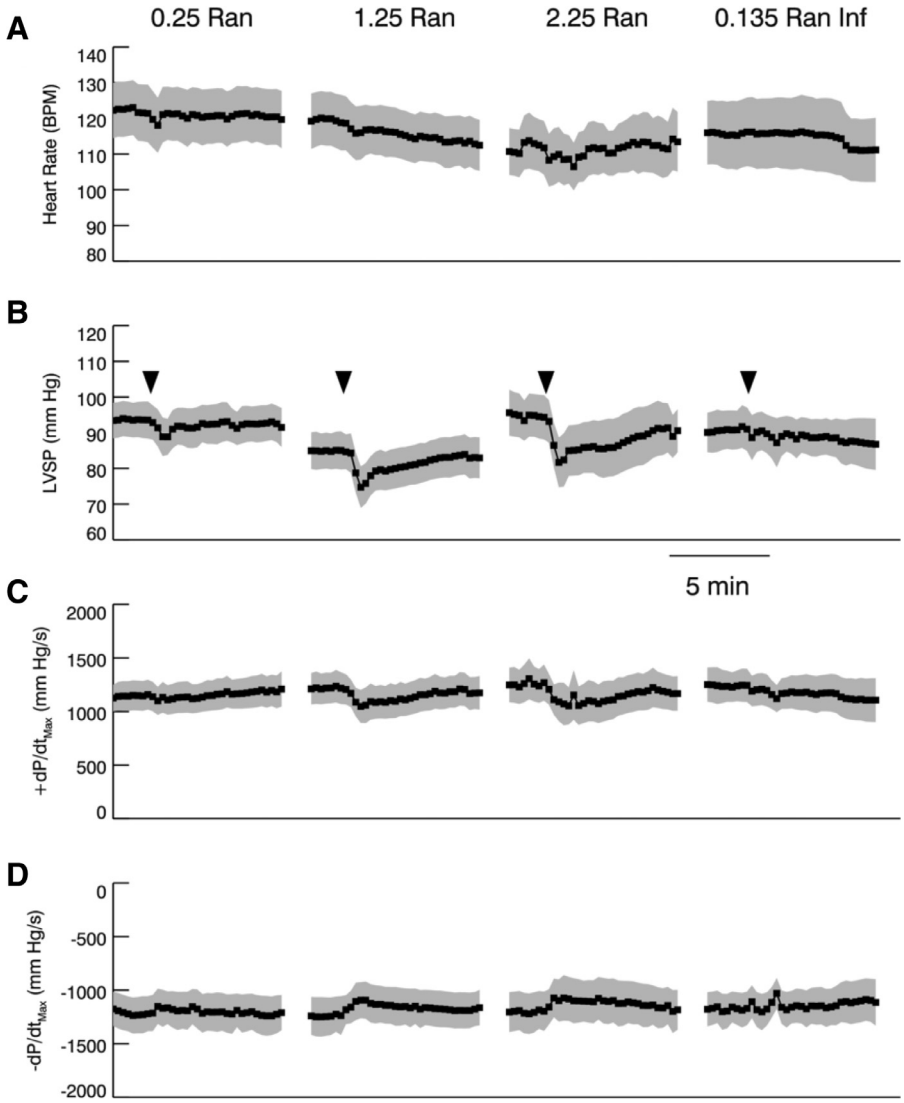

Fig. 2. Transient hemodynamic changes after bolus ranolazine (Ran) in HF swine. A, heart rate. B, left ventricular peak systolic pressure (LVSP). C, $+dP/dt_{max}$; D, $-dP/dt_{max}$. Each point represents the mean of 9 animals with ± SEM indicated by shading. Arrowheads in panel B show the time of bolus injection (0.25, 1.25 and 2.25 mg/kg Ran) or the start of sustained infusion (inf, 0.135 mg/kg/min). Records begin immediately after boluses or beginning infusion to illustrate transients; time scale (horizontal axis) is not continuous. Abbreviations as in Fig. 1.

Table 2. Hemodynamic Responses in Swine With Heart Failure or Control Swine to Infused Late-Na^+ Channel Blockers

		Base/Final	Δ ± SEMD	95% CI −	95% CI +			Base/Final	Δ ± SEMD	95% CI−	95% CI+
A. Ranolazine											
HF N = 9	HR, bpm	123/114	−10 ± 6	−22.1	2.1	Control N = 6	HR, bpm	118/124	5 ± 4	−3.03	13.03
	LVSP, mmHg	9/93	−1.5 ± 4.3	−10	7		LVSP, mmHg	122/114	−8.2 ± 3.1	−14.25	−2.15
	LVEDP, mmHg	25/24	−1.1±2.5	−3.6	104		LVEDP, mmHg	18/18	0.2 ± 1.8	−3.3	3.7
	$+dP/dt_{max}$	1243/1418	176 ± 133	−84.5	436.5		$+dP/dt_{max}$	2371/2629	258 ± 186	−105.9	621.9
	$-dP/dt_{max}$	−1409/−1420	−11 ± 134	−272.9	250.9		$-dP/dt_{max}$	−3526/−3191	335 ± 275	−203.1	873.0
	τ, s	0.13/0.14	−0.008 ± 0.03	−0.065	0.049		τ, s	0.033/0.032	−0.002 ± 0.003	−0.07	0.003
B. Mexiletine											
HF N=7	HR, bpm	117/117	0.3 ± 6	−10.6	11.2	Control N = 4	HR, bpm	107/119	13 ± 9	−5.2	31.2
	LVSP, mmHg	97/103	7.4 ± 4.0	−0.5	15.3		LVSP, mmHg	106/126	20 ± 9	1.4	38.6
	LVEDP, mmHg	27/30	3.4 ± 2.6	−1.7	8.5		LVEDP, mmHg	19/19	1.0 ± 0.8	−0.49	2.49
	$+dP/dt_{max}$	1139/1303	164 ± 72	23.7	304.3		$+dP/dt_{max}$	2228/2734	506 ± 249	17.6	994.4
	$-dP/dt_{max}$	−1181/−1207	−25 ± 77	−176.5	126.5		$-dP/dt_{max}$	−2864/-3746	−882 ± 473	−1809.6	45.6
	τ, s	0.13/0.21	0.08 ± 0.08	−0.081	0.241		τ, s	0.029/0.031	0.003 ± 0.003	−0.002	0.008
C. Ranolazine + ivabradine											
HF N=7	HR, bpm	79/72	−7.3 ± 3.0	−13	−1.6						
	LVSP, mmHg	105/105	−0.06 ± 3.4	−6.64	6.76						
	LVEDP, mmHg	32/31	−0.95±3.8	−6.05	7.95						
	$+dP/dt_{max}$	1431/1676	246 ± 244	−232.9	724.9						
	$-dP/dt_{max}$	−1463/−1331	133 ± 128	−114.9	380.9						
	τ, s	0.17/0.25	0.077 ± 0.01	−0.043	0.197						

Responses to ranolazine (A), mexiletine (B) or ranolazine after prebaseline ivabradine (C) are shown for treatment subgroups (size = N) with HF (left columns) or no HF (controls, right columns). Mean subgroup predrug baselines (Base) are paired with values after completion of drug administration (Final). Changes from baseline to completion of drug administration were calculated for each animal and averaged by subgroup. In most cases, mean differences (Δ)—shown with standard error of the mean difference (± SEMD) and 95% confidence intervals (CI)−were not statistically different from 0; that is, 0 difference fell between lower limit (95% CI−) and upper limit (95% CI+) of the respective CI. Exceptions were: 2%−11% mean rise in LVSP for ranolazine control; 2%−16% mean fall in HR for ranolazine + ivabradine; 0−27% mean rise in $+dP/dt_{Max}$ for mexiletine HF; and 0−45% mean rise in $+dP/dt_{Max}$ and 1%−36% mean rise in LVSP for mexiletine control. Abbreviations as in Table 1.

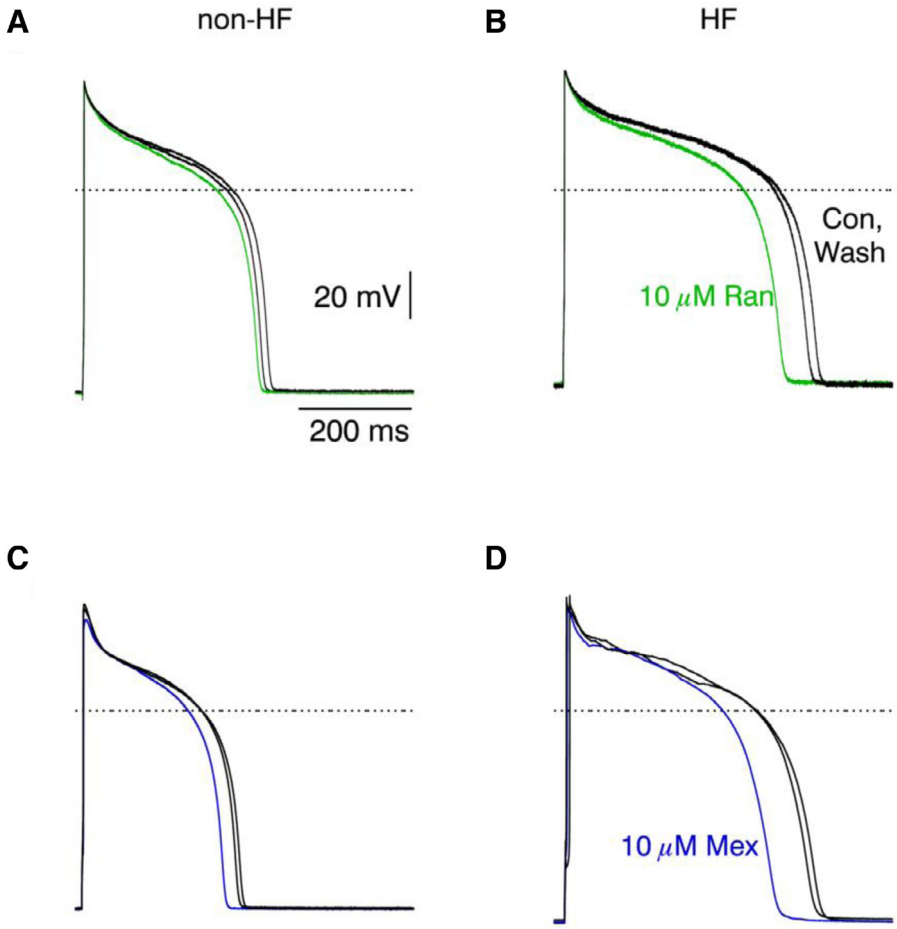

Fig. 3. Action potential (AP) shortening in the presence of blockers of late Na^+ current. A and C: APs recorded from control (non-HF) ventricular cardiomyocytes. B and D: APs from heart failure (HF) cardiomyocytes. Exposure to ranolazine (left line = 10 μM Ran, A and B) and mexiletine (left line = 10 μM Mex, C and D), each compared to pre-exposure (Con) and wash-out (Wash). Dotted horizontal lines indicate 0 mV. [Colors should be utilized in Web presentation]

of 0 fell within the 95% uncertainty limits calculated from data variability, satisfying the null hypothesis. Contractile responses to ranolazine ($+dP/dt_{max}$) were not correlated with a measure reflecting severity of baseline HF (LVEDP). Similar observations were evident in the control swine. The single exception was systolic pressure in control swine, with a 2%−11% average decline after ranolazine. Lack of detectable treatment effect on contracility remained evident in a separate group of animals with HF given ranolazine when $I_{Na,late}$ was maximized by slowing heart rate decreased by 29 beats per min (mean) with prior bolus ivabradine (n = 7) (Table 2C). A 2%−16% decline in heart rate was noted after ranolazine plus ivabradine in swine with HF, but all other mean changes—including those directly related to contractility—were not different from 0.

Effects of Mexiletine Administration

Similar responses were observed in swine given mexiletine. All remained in sinus rhythm without consistent change in ECG parameters during the course of the study. Mexiletine plasma concentrations at end-infusion were 6.4 ± 1.3 μg/mL (SEM), equivalent to 27.9 ± 5.9 μM (n = 8, HF and non-HF pooled). Paired comparisons between measurement at pretreatment baseline and maximal mexiletine treatment at completion of infusion generally showed no detectable change in heart rate or any LV pressure parameter for animals with HF (n = 7) (Table 2B). As with ranolazine, the mean change of 0 usually fell within the 95% uncertainty limits defined by data variability, satisfying the null hypothesis. Only mean $+dP/dt_{Max}$ in animals with HF rose 0−21% after mexiletine. Contractile responses to mexiletine ($+dP/dt_{max}$) were not correlated with severity of baseline HF (LVEDP). Similar observations were evident in control swine (n = 4); in this group mean $+dP/dt_{Max}$ after mexiletine rose 0−45% and LVSP 1%−36%.

Patch-clamp Studies of Isolated Cardiomyocytes

Patch-clamp studies of cardiomyocytes isolated from the left ventricles of controls and swine with HF demonstrated the effectiveness of relevant concentrations of ranolazine or mexiletine by reducing $I_{Na,late}$ and shortening APD, particularly when prolonged in the presence of HF (Fig. 3). As expected, HF cells had increased APD attenuated by 10 μM of either $I_{Na,late}$ inhibitor, confirming the

Table 3. Action Potential Duration After 10 μM Ranolazine at Slower and Faster Pacing

	0.2 Hz		1 Hz	
Pacing frequency	Control	HF	Control	HF
N	5	6	4	6
Mean APD_{90} ± SEM	513 ± 113	1021 ± 149	358 ± 32	682 ± 108
% APD shortening	5.8 ± 2.6	17.9 ± 3.1*	2.9 ± 1.2	11.2 ± 2.6*

APD_{90}, action potential duration at 90% repolarization (msec); control, cardiomyocytes from LV without heart failure; HF, cardiomyocytes from LV showing heart failure; N, number of studies; SEM, standard error of the mean.

*$P \leq 0.01$ vs preranolazine.

Note: Mean predrug APD values appear in the upper row. Mean percent shortening ± SEM after ranolazine exposure are shown.

contribution of $I_{Na,late}$ to APD prolongation in HF. At slower pacing rates, APD was even longer at baseline and more reduced in the presence of 10 μM ranolazine (Table 3). These findings suggest a greater magnitude of $I_{Na,late}$ during bradycardic HF and potentially more robust influence of $I_{Na,late}$ inhibition when sinus rates are not elevated.

Direct measurement of $I_{Na,late}$ supported results obtained by APD recordings. Baseline $I_{Na,late}$, measured 50 msec after onset of depolarization, averaged 0.23 ± 0.02 pA/pF for control myocytes (n = 84) and 0.32 ± 0.02 pA/pF for HF myocytes (n = 137) ($P < 0.001$), confirming the expected larger $I_{Na,late}$ in HF myocytes. Mean cell capacitance was 94 ± 1 μF for controls and 111 ± 11 μF for HF myocytes ($P < 0.001$), consistent with hypertrophy of HF myocytes. The addition of ranolazine 10 μM to HF myocytes reduced $I_{Na,late}$ at 50 msec by 74% ± 6% (n = 5) ($P < 0.001$), demonstrating effective blockade of $I_{Na,late}$ at concentrations employed in vivo.

Discussion

We sought to determine the hemodynamic impact of acute blockade of the $I_{Na,Late}$ current in a tachypaced swine model with multiple hemodynamic features of severe systolic heart failure (Table 1). To place such findings in context, we also assessed hemodynamic responses to ranolazine or mexiletine in swine without HF.

Paired analysis of hemodynamic performance before and after ranolazine indicated that this drug in doses sufficient to block $I_{Na,Late}$ current induced no detectable changes in animals with advanced HF, even when this current was maximized by superimposed bradycardia. Lack of hemodynamic change after ranolazine in HF swine resembled the results observed in the control swine. Mexiletine generally showed the same outcomes as ranolazine. Although mexiletine appeared to increase $+dP/dt_{Max}$, associated findings do not support a general influence on hemodynamic performance. A true mean change of 0 after either drug treatment was compatible with observed results for most parameters.

The major findings of this study indicate that acute inhibition of $I_{Na,Late}$ current with either ranolazine or mexiletine had no measurable deleterious impact on parameters of systolic function despite the alterations of HF, supporting possible safe use of these drugs in the presence of HF and high risk for accelerated hemodynamic deterioration or arrhythmia. Contrary to our initial hypothesis, we found no improvement in LV end-diastolic pressure or indices of LV relaxation in our intact swine model, suggesting that these potent $I_{Na,Late}$ inhibitors do not cause meaningful decrement in diastolic dysfunction during HF. Moreover, improved diastolic relaxation with $I_{Na,Late}$ inhibition was not elicited by the concurrent use of ivabradine to enhance $I_{Na,Late}$ through the slowing of the sinus rate to usual clinical values. Thus, improvement was not observed, even when conditions were optimized in the HF model to demonstrate drug-induced benefit in relaxation.

Our patch-clamp results confirmed that $I_{Na,Late}$ contributes to HF-related prolongation of APD in isolated cardiomyocytes[23] and also confirmed that effective inhibition of $I_{Na,Late}$ by ranolazine shortens the APD prolonged in association with HF.[8] Plasma drug levels in vivo were similar to those achieved in vitro, indicating that substantial levels of inhibition of $I_{Na,Late}$ current were present in vivo and in vitro. Our in vitro data further showed that stimulus or pacing frequency modulates the availability of $I_{Na,Late}$ in swine HF myocytes and demonstrated the greater ability of blockers of $I_{Na,Late}$ to shorten the APD when pacing frequency is slowed.

Importance of the Late Na^+Current in Heart Failure

Although the mechanism underlying the increase in $I_{Na,Late}$ in the failing heart has not yet been fully elucidated, $I_{Na,Late}$ has been shown to be upregulated by Ca^{+2} activation of CaM-Kinase II, hypoxia and reactive oxygen species and is modulated by changed Na^+ channel β subunits and disruption of cytoskeletal elements, conditions commonly present during HF.[24] These are likely factors in the increased $I_{Na,Late}$ observed in our porcine cardiomyocytes. Despite the implied increased $I_{Na,Late}$ during HF, our results in an intact model of HF in swine showed no significant effects on LV pressure parameters or heart rate with administration of $I_{Na,Late}$ inhibitory doses of ranolazine or mexiletine. In the presence of multiple factors favoring reduced diastolic myocardial elasticity during HF,[25] inhibition of $I_{Na,Late}$ may fail to lower myoplasmic Ca^{+2} levels near sarcomeres sufficiently to relax diastolic tension during HF induced by tachypacing.

Ranolazine and Mexiletine in Heart Failure

Ranolazine is a fairly specific blocker of the late Na^+ current at low (2−5 μM) concentrations. At higher concentrations, it also inhibits the early Na^+ current, the hERG channel, the L-type Ca^{2+} channel, and the Na^+/Ca^{2+} exchanger.[26] Ranolazine has been approved by the Food and Drug Administration as an antianginal and has been proposed as a treatment for diastolic dysfunction in HF. Clinical benefit may accrue through ranolazine's ability to lower myoplasmic Na^+ levels, reduce Na^+-Ca^{+2} exchange and, accordingly, lower diastolic Ca^{+2}. Particularly during myocardial ischemia, these changes may attenuate excessive myocardial oxygen utilization and Ca^{+2} overload

and, thereby, relax diastolic tension and improve coronary blood flow.[24] Ranolazine may also modify myofilament Ca^{2+} responsiveness to augment diastolic relaxation.[27] In the RALI-DHF clinical trial,[28] acute administration of ranolazine was found to lower pulmonary artery pressure significantly during pacing with no change in LV end-diastolic pressure in patients with HF who had preserved ejection fraction. Ranolazine has also been shown to reduce diastolic frequency-dependent tension in muscle strips from failing human hearts.[29] A concern has been that reducing Ca^{+2} overload to improve of diastolic dysfunction could inadvertently compromise systolic performance in severely weakened hearts. Earlier clinical studies indicated acutely administered mexiletine may exert such an effect,[30,31] although more recent experience shows that hemodynamic deterioration is uncommon when mexiletine is given to patients with severe cardiac dysfunction.[32] The lack of adverse consequences with $I_{Na,Late}$-blocking doses of ranolazine or mexiletine during advanced HF demonstrated in our animal studies suggests that concern regarding hemodynamic compromise due to systolic contractile insufficiency associated with drug-induced inhibition of $I_{Na,Late}$ may be unwarranted. This conclusion is bolstered by the lack of increased numbers of hospitalizations due to HF among high-risk patients given ranolazine during the recently-published RAID trial.[13] Hemodynamic deterioration sometimes observed in patients with HF given mexiletine[30–32] may be due to other toxic properties of this drug.

Limitations

The model employed in this study is based on HF induced by sustained tachypacing. Metabolic circumstances—and drug responsiveness—will likely differ in other conditions leading to systolic dysfunction and other causes of HF. Ranolazine may have special value for HF in the context of myocardial ischemia, a possibility supported by benefits shown in dogs subjected to coronary microemboli.[33] However, the basic concern addressed in our study—critical loss of contractile function due to attenuation of $I_{Na,Late}$ and resultant decrement in Ca^{+2} release—appears to be unlikely in view of the evidence presented by this study.

An additional consideration is the brevity of drug exposure utilized in our model. Longer term administration of ranolazine or mexiletine might elicit responses different from those shown in this study. Moreover, the use of pentobarbital for anesthesia in our model likely exerted a depressant effect on myocardial contractility and may have affected drug responses. Further experimentation is needed to address these issues.

Although most of the observed changes in hemodynamic parameters were consistent with the hypothesis of no change, the confidence intervals of tau for the HF treatment subgroups were particularly wide. The data for τ are consistent with no change, but they are also consistent with changes that could be important.

Results from animal models require confirmation in clinical settings. In particular, the finding that inhibition of $I_{Na,Late}$ does not worsen advanced systolic dysfunction must be interpreted with caution when applied to clinical circumstances.

Conclusions

Patients with HF and significant systolic dysfunction are at risk of severe ventricular arrhythmia, in part due to excessive intracellular Na^+ influx and the resultant increase in intracellular Ca^{+2}. Recent clinical trials have demonstrated the antiarrhythmic efficacy of ranolazine and other blockers of abnormal Na^+ entry. Such therapy may be particularly appropriate to diminish arrhythmic and ischemic hazard in HF. However, patients with advanced HF might deteriorate if this blockade reduced myocyte Ca^{+2} with increased loss of systolic contractility. In a relevant animal model, our results showed blocking doses of ranolazine or mexiletine did not worsen badly deteriorated parameters of LV contractile function. These drugs also failed to improve markers of diastolic relaxation, as might occur with reduced myocyte Ca^{+2}. While suggesting that inhibition of $I_{Na,Late}$ with ranolazine or mexiletine may be safe for patients with advanced HF, our findings highlight the need for clinical investigation to confirm the lack of adverse circulatory consequences and, perhaps, to identify a unique benefit incident to blockade of late Na^+ influx in patients with advanced HF.

Disclosures

The opinions and assertions expressed herein are those of the authors and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense.

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Supplementary materials

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