Published in final edited form as:

Heart Rhythm. 2020 February ; 17(2): 332–340. doi:10.1016/j.hrthm.2019.09.008.

Ondansetron effects on apamin-sensitive small conductance calcium-activated potassium currents in pacing induced failing rabbit hearts

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Abstract

Background: Ondansetron, a widely prescribed antiemetic, has been implicated in drug-induced long QT syndrome. Recent patch clamp experiments have shown that ondansetron inhibits the apamin sensitive calcium activated potassium current (I_{KAS}).

Objective: To determine if ondansetron causes action potential duration (APD) prolongation by I_{KAS} inhibition.

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Disclosures: None

Methods: Optical mapping was performed in rabbit hearts with pacing induced heart failure (HF) and in normal hearts before and after ondansetron (100 nM) infusion. APD at 80% repolarization (APD₈₀) and arrhythmia inducibility were determined. Additional studies with ondansetron were performed in normal hearts perfused with a hypokalemia (2.4 mM) solution before or after apamin.

Results: The QTc interval in HF was 326 ms [95% CI, 306–347] at baseline and 364 ms [95% CI, 351–378] after ondansetron ($p < 0.001$). Ondansetron significantly prolonged the APD₈₀ in the HF group and promoted early afterdepolarizations, steepened the APD restitution curve and increased ventricular vulnerability. VF was not inducible in the HF ventricles at baseline, but after ondansetron infusion, VF was induced in 5 of 7 ventricles ($P = 0.021$). In hypokalemia, apamin prolonged the APD₈₀ from 163 ms [CI, 146–180] to 180 ms [95% CI, 156–204] ($P = 0.018$). Subsequent administration of ondansetron failed to further prolong APD₈₀ (180 ms [95% CI, 156–204] vs 179 ms [95% CI, 165–194], $P = 0.789$). The results were similar when ondansetron was administered first followed by apamin.

Conclusions: Ondansetron is a specific I_{KAS} blocker at therapeutic concentrations. Ondansetron may prolong the QT interval in HF by inhibiting SK channels which increases the vulnerability to ventricular arrhythmias.

Keywords

ondansetron; electrophysiology; heart failure; ventricular fibrillation; optical mapping

Introduction

Ventricular arrhythmia is a major cause of death in patients with heart failure (HF).¹ Multiple randomized clinical trials^{2–4} conducted in patients with HF documented increased ventricular arrhythmia or mortality in patients randomized to the drug treatment arm. These results suggested that HF predisposes patients to drug-induced arrhythmias.⁵ Ondansetron, a 5-HT₃-receptor antagonist that is a widely prescribed antiemetic, has been implicated in drug-induced long QT syndrome (diLQT) especially in patients with HF.⁶ A recent study confirmed that clinical concentrations of ondansetron can cause action potential duration (APD) prolongation.⁶ This study showed that 31% of patients in the HF group met gender-related thresholds for a prolonged QTc.⁶ Because ondansetron blocks I_{Kr} and I_{Ks} only at concentrations much higher than the therapeutic range,⁷ the mechanisms by which therapeutic levels of ondansetron prolongs the QT interval remains unclear. Apamin-sensitive small conductance calcium activated potassium (SK) current (I_{KAS}) has been shown to be important in ventricular repolarization.^{8–10} Although SK channels conduct little to no current in normal ventricles,^{8, 11, 12} previous studies have demonstrated a marked I_{KAS} upregulation in failing hearts, as well as during bradycardia and during hypokalemia in normal ventricles.^{8, 9, 13} Increased activation of I_{KAS} may counteract the excess action potential prolongation typically associated with these conditions and help maintain the repolarization reserve.¹⁴ Inhibiting I_{KAS} has been shown to lengthen the APD and QTc and increase ventricular fibrillation (VF) vulnerability with an increase in the frequency of EADs and TdP.^{14, 15} A recent study that performed patch-clamp studies in human embryonic kidney (HEK) 293 cells that expressed SK channels showed that ondansetron inhibited the

SK current at therapeutic concentrations. Based on these data, we hypothesized that ondansetron at therapeutic concentrations would have similar characteristics to apamin and cause APD prolongation by I_{KAS} inhibition in failing ventricles and increase VF vulnerability. The purpose of this study is to use optical mapping to determine the electrophysiological characteristics of cardiac tissue during ondansetron infusion, and to investigate if ondansetron inhibits I_{KAS} in a rabbit model of HF and hypokalemia, but not in normal rabbit ventricles.

Methods

This study protocol was approved by the Institutional Animal Care and Use Committee of Indiana University School of Medicine and the Methodist Research Institute, and conforms to the NIH Guide for the Care and Use of Laboratory Animals. Heart failure was induced in ten New Zealand white rabbits via rapid ventricular pacing.⁸ Among them, 8 completed the pacing protocol and developed HF. Seven rabbits with structurally normal hearts were used as controls. An additional 6 rabbits with structurally normal hearts were used for experiments within a hypokalemic environment. After HF was induced and in controls, hearts were excised and Langendorff perfused with oxygenated Tyrode's solution. Optical recordings were made from a 100×100 pixel area with a spatial resolution of 0.35×0.35 mm² per pixel, and sampled at 2ms/frame.⁸ A pseudoECG was obtained with widely spaced bipolar electrodes to determine the QT interval and ventricular rhythm. Cardiomyocytes for patch-clamp experiments to measure whole cell I_{KAS} were acquired from 1 HF heart and 2 structurally normal hearts. A detailed methods section is included in the Online Supplement.

Statistical Analysis

Data are presented as mean and 95% confidence interval (CI). Paired Student t tests were used to compare variables measured at baseline and after drug infusion. Categorical parameters between groups comparing VF vulnerability were compared by the Fisher exact test. The P values are corrected for multiple comparisons in relevant analyses using Bonferroni adjustment. A 2-sided P value of 0.05 was considered statistically significant.

Results

All rabbits that survived the rapid pacing protocol (n=7) showed clinical signs of HF as previously described.⁸ Table 1 shows the echocardiographic data before and after the development of HF. As the results in the table show, significant LV dysfunction developed with ventricular pacing.

Effects of ondansetron on QT interval

A pseudoECG was obtained to determine the QT interval. As figure 1 shows, in failing hearts ondansetron significantly prolonged the QT interval compared to baseline. Figure 1B shows the effects of ondansetron on the QT and corrected QT (QTc) intervals in all 7 hearts studied. Overall during ondansetron infusion, the QT interval increased (baseline vs ondansetron, 196 ms [95% CI, 181–210] vs 237 ms [95% CI, 195–279, p=0.02] and the QTc increased (baseline vs ondansetron, 326 ms [95% CI, 306–347] vs 364 ms [95% CI,

351–378], $p<0.001$] during normal sinus rhythm in failing hearts. Ondansetron didn't prolong either the QT or the corrected QT (QTc) intervals in all 5 normal hearts (figure 1 C and D). The QT interval (baseline vs ondansetron, 189 ms [95% CI, 180–199] vs 192 ms [95% CI, 181–203, $p=0.402$] and the QTc didn't increase (baseline vs ondansetron, 319 ms [95% CI, 302–336] vs 322 ms [95% CI, 306–338], $p=0.675$] during normal sinus rhythm.

Effects of ondansetron on APD

Figure 2 shows APD maps at baseline and after ondansetron and the APD maps from recordings made in the HF model. Figure 2B shows the mean APD₈₀ without and with ondansetron. Ondansetron prolonged APD₈₀ at all PCLs, however, the effects were more apparent at longer PCLs. At the PCL of 300 ms, ondansetron prolonged the APD₈₀ from 156 milliseconds (95% CI, 150–161) to 173 ms (95% CI, 167–179; $P<0.001$). The average magnitude of APD₈₀ prolongation at 300 ms PCLs was 18 ms (95% CI, 16–20). The percentage of prolongation at PCLs of 300 ms was 11.34% (95% CI, 10.06–12.6). APD heterogeneity has been recognized as an important factor contributing to ventricular arrhythmia. We used the correlation of variance generated from the optically imaged region to quantify APD heterogeneity. Figure 2C shows that ondansetron significantly increased the correlation of variance of APD₈₀ at all PCLs. In HF ventricles after ondansetron infusion, APD₈₀ distribution became more heterogeneous than at baseline. Figure 3 shows ondansetron did not significantly prolong the APD₈₀ in normal ventricles and had no significant effect on the heterogeneity of the APD₈₀.

Effect of ondansetron on EAD and VF vulnerability

Figure 4A shows the representative examples of optical mapping traces at baseline and after addition of ondansetron in the HF model. Ondansetron significantly prolonged the APD at a PCL of 300 ms. At baseline, there was no spontaneous or pacing-induced TdP with an S1/S2 pacing protocol. After ondansetron infusion, either spontaneous, pacing-induced TdP, or EADs were observed in 4 ventricles ($p=0.035$, Figure 4C). Figure 4B shows pacing induced TdP after ondansetron administration. APD₈₀ maps of the S1 and S2 show an increase in APD heterogeneity prior to TdP initiation. TdP was not induced in structurally normal hearts either before or after ondansetron infusion. Action potential duration restitution (APDR) curves were determined at a basal and apical area over the LV in each heart studied. In a representative ventricle (Figure 5A), the APDR slope consistently showed that ondansetron prolonged APD₈₀ at both long (400 ms) and short (130 ms) PCLs. For the 7 hearts with ventricular pacing, I_{KAS} blockade increased the maximal slope of APDR from (1.06 [95% CI, 0.87–1.24] at baseline to 1.71 [95% CI, 1.28–2.15], $p=0.003$ Figure 5B) after ondansetron at the apical area, and increased the maximal slope of APDR from (1.12 [95% CI, 1.00–1.26] at baseline to 1.65 [95% CI, 1.32–2.03], $p=0.019$ Figure 5B) at the basal area. Also ondansetron increased the pacing cycle length threshold of APD alternans from 177 ms [95% CI, 158–196] to 204 ms [95% CI, 181–228], $p<0.001$ (Fig 5C). At baseline, no VF was inducible in the HF ventricles with extrastimuli, but after ondansetron infusion, VF was induced in 5 of the 7 failing ventricles ($P=0.021$). There was no spontaneous VF either before or after ondansetron administration.

Ondansetron is a selective SK current blocker

It has been previously shown that I_{KAS} is upregulated in both failing ventricles and in normal ventricles within a hypokalemic environment.^{9, 16} To investigate the effect of ondansetron on I_{KAS} , in three of the 7 failing hearts, the pacing protocol with ondansetron (100 nmol/L) was performed first, then apamin (100 nmol/L) was added and the protocol was repeated. Figure 6A shows that ondansetron prolonged the APD₈₀ from 155ms [CI, 136-173] to 173 ms [CI, 152-194] (P=0.002), but subsequent administration of apamin failed to further prolong APD₈₀ (173 ms [CI, 152-194] vs 174 ms [CI, 155-193], P=NS). In 3 normal ventricles perfused with a hypokalemic Tyrode's solution, ondansetron prolonged the APD₈₀ from 148 ms [CI, 143-154] to 166 ms [CI, 159-174] (P=0.025). Subsequent administration of apamin failed to further prolong APD₈₀ (166 ms [CI, 159-174] vs 168 ms [CI, 163-173] ms, P=0.13). In an additional 3 hypokalemic ventricles, apamin was added to the perfusate first and the APD₈₀ prolonged from 163 ms [CI, 146-180] to 180 ms [CI, 156-204] (P=0.018). Subsequent administration of ondansetron failed to further prolong APD₈₀ (180 ms [CI, 156-204] vs 179 ms [CI, 165-194], P=0.789). These data show that ondansetron has a similar effect on the APD as apamin within substrates known to have increased I_{KAS} suggesting that ondansetron is inhibiting I_{KAS} . The time course of ondansetron on the APD₈₀ shows that the APD₈₀ was significantly prolonged 15 minutes after beginning infusion and became stable after 30 minutes (Fig1 in the online-only Data Supplement).

To further investigate the effects of ondansetron on I_{KAS} , we determined the efficacy of ondansetron in inhibiting SK channels in isolated ventricular myocytes. Exposure of myocytes to 100 nM ondansetron unveiled a current with I_{KAS} -typical properties (Figure 7 A & C). Ondansetron applied in the continuing presence of 100 nM apamin was without effect (Figure 7 B & D), indicating that ondansetron selectively reduced I_{KAS} under the experimental conditions used.

Discussion

The main finding of this study was that infusion of ondansetron lengthened the APD within the HF substrate, resulting in an increased QT interval. In addition, the slope of APD restitution was increased correlating to the occurrence of EADs and an increased vulnerability to VF. When compared to apamin, a specific I_{KAS} blocker, therapeutic concentrations of ondansetron had similar effects on the APD₈₀ that was not further enhanced with apamin. This data suggests that therapeutic concentrations of ondansetron lengthens the APD through inhibiting I_{KAS} which may promote diLQT and increase vulnerability to VF within substrates known to have increased I_{KAS} .

SK expression in hypokalemia and in the heart failure substrate

Recent studies have shown that I_{KAS} is upregulated in failing ventricular cardiomyocytes,^{8, 15-17} along with increased SK channel protein expression and enhanced sensitivity to intracellular Ca^{2+} . In addition, Chua et al previously showed that I_{KAS} was heterogeneously upregulated in a rabbit heart failure model.⁸ This heterogeneity was observed both transmurally and within the same surface. Transmural heterogeneity of I_{KAS}

expression has also been shown in cardiomyocytes from heart failure transplant recipients.¹⁶ More recently, Bonilla et al¹⁸ and Ni et al¹⁷ confirmed these observations by showing that apamin significantly prolonged APD in failing human and canine ventricular cardiomyocytes, along with the increased expression of SK channel protein in failing ventricles. In addition to HF, I_{KAS} has been shown to be activated during hypokalemic conditions.⁹ In the current study, as shown in Figure 6e, the APD₈₀ was heterogeneously lengthened after apamin in hypokalemic conditions, indicating a heterogeneous upregulation of I_{KAS} which supports the previous studies.

Ondansetron as an I_{KAS} blocker

A previous patch clamp study showed ondansetron blocks I_{Kr} only at high concentrations, with IC₅₀ of 0.81 μ M.⁷ In addition, ondansetron blocked < 30% of I_{Ks} at concentrations as high as 3 μ M. Based on this study, therapeutic concentrations of ondansetron do not have a significant effect on I_{Kr} and I_{Ks} . We first administered ondansetron at lower therapeutic concentrations (100 nmol/L) to failing rabbit hearts,¹⁹ which is a substrate known to have increased I_{KAS} .^{8, 15} Subsequent analysis showed a significant increase in APD. We then administered 100 nmol/L of apamin in which there was no significant change in APD. To confirm that ondansetron inhibits I_{KAS} , we then performed additional experiments in which apamin was given first, followed by ondansetron. Apamin significantly increased APD compared to baseline, but adding ondansetron after apamin showed no additional increase to the APD. Since ondansetron failed to further lengthen the APD after apamin, these data suggest that ondansetron at 100 nM specifically inhibits I_{KAS} .

I_{KAS} and drug safety

I_{KAS} upregulation is theorized to be the mechanism by which failing ventricles maintain repolarization reserve and prevent afterdepolarizations. The importance of I_{KAS} in human ventricular repolarization is supported by a recent study¹⁶ that showed apamin prolonged APD in failing human ventricular cells by a mean of 11.8%. Inhibiting I_{KAS} within this substrate produced an increase in EADs, TdP, and VF vulnerability.^{14, 15} Recently, we found that a custom Next Generation Sequencing targeted enrichment and Sanger sequencing approach revealed a KCNN2 c.1509C>G (p.F503L in NM_021614.3) variant in a 52-year-old female whose QTc prolonged from 450 ms to 560 ms after taking ondansetron. Studies using patch clamp techniques demonstrated that the p.F503L KCNN2 increased the Ca²⁺ sensitivity of SK2 channels and indicated that ondansetron is an effective I_{KAS} blocker similar to apamin.²⁰ In addition, we recently demonstrated that inhibiting I_{KAS} in a cardiac memory model increased the vulnerability to ventricular arrhythmias.²¹ The data presented in this study suggests that the underlying mechanism of the QTc prolongation is through inhibiting I_{KAS} . These studies support that when I_{KAS} is inhibited within substrates in which I_{KAS} is upregulated to maintain the repolarization reserve, the risk for initiation of ventricular arrhythmias is increased.

Clinical implications

Because I_{KAS} is absent in cardiomyocytes isolated from non-failing ventricles,¹² I_{KAS} blockers might be clinically useful as an atrial-selective antiarrhythmic agent.²² However, known I_{KAS} blockers such as apamin are neurotoxins that cannot be used in humans. In

comparison, ondansetron at the therapeutic dose has minimal neurological side effects. An extensive literature search has showed no case reports of seizure disorder induced by oral ondansetron. The present study showed that ondansetron had minimal effects in normal ventricles but profound proarrhythmic effects on failing ventricles. These findings suggest that ondansetron might be an atrial selective antiarrhythmic agent only in patients with normal ventricles. It may not be safe in patients with HF or hypokalemia. Clinical studies have shown that intravenous doses of ondansetron can significantly prolong QT intervals in patients with additional cardiovascular risk factors for Torsades de Pointes.⁶ However, others found no reported cases of Torsades de Pointes ventricular arrhythmias induced by orally administered ondansetron.^{23, 24} Prospective clinical studies are needed to define the antiarrhythmic potential and proarrhythmic risks of ondansetron administration in patients with cardiac arrhythmias.

Limitations

We did not determine the distribution of I_{KAS} channels with immunohistochemistry. However, two other studies^{8, 15} have documented the heterogeneous upregulation of I_{KAS} in failing ventricles, and a recent patch-clamp study demonstrated ondansetron's effects on I_{KAS} in HEK293 cells.²⁰ Another limitation of the study is that the mapping was performed only on the epicardial surface. These findings may not be applicable to the mid-myocardial or endocardial layers of the myocardium. We have not tested ondansetron in arrhythmia models to test its antiarrhythmic efficacy. Like apamin, ondansetron may be antiarrhythmic in specific conditions, such as electrical storm when recurrent VF occurred in failing ventricles due to I_{KAS} activation.⁸ However spontaneous VF was an unusual event even in failing rabbit ventricles^{8, 25} and we did not observe any episodes of spontaneous VF either before or after ondansetron in this group of failing ventricles. A large series of animals will be needed to determine if ondansetron can suppress spontaneous VF.

Conclusions

Ondansetron has similar characteristics to apamin within substrates known to have increased I_{KAS} activity. This supports the hypothesis that ondansetron blocks I_{KAS} leading to APD prolongation and lengthening of the QT interval. This inhibition of I_{KAS} decreases the repolarization reserve and increases the vulnerability to VF. However, ondansetron which is currently used clinically to reduce nausea, may also have anti-arrhythmia characteristics within certain substrates based on its APD lengthening characteristics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Yudong Fei, MD for his assistance in the patch clamp studies.

Sources of Funding

This study was supported in part by National Institutes of Health grants P01 HL78931, R01 HL71140, R41 HL124741 and R42 DA043391, R56 HL071140, U18 TR002208-01, R01 HL139829, a Medtronic-Zipes

Endowment, the Charles Fisch Cardiovascular Research Award endowed by Dr Suzanne B. Knoebel of the Krannert Institute of Cardiology, and the Indiana University Health-Indiana University School of Medicine Strategic Research Initiative.

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Figure 1. Effect of Ondansetron on QT interval. Representative pseudoECG traces of QT interval in a failing (Panels A and B) and structurally normal hearts (Panels C and D) before and after 100 nmol/L of ondansetron. Ondansetron significantly prolonged the QT and corrected QT interval (QTc) in failing hearts but not in structurally normal hearts.

Figure 2.

Effects of ondansetron on APD and APD₈₀ heterogeneity at different pacing cycle lengths in failing ventricles. **A**. Representative membrane potential traces and APD₈₀ maps at baseline and in the presence of ondansetron (100 nmol/L). The magnitude of APD prolongation was more prominent at long PCLs than at short PCLs (**B**, **D**). **C**. Effect of ondansetron on APD₈₀ heterogeneity at different PCLs in failing ventricles. Ondansetron significantly increased the correlation of variance of APD₈₀. Δ APD = APD₈₀ after ondansetron - APD₈₀ at baseline.

Figure 3.

Effects of ondansetron APD at different pacing cycle lengths in normal ventricles. **A.** Representative membrane potential traces and APD₈₀ maps at baseline and in the presence of ondansetron (100 nmol/L). **B.** Summary data showing that ondansetron only prolonged the APD₈₀ at a PCL of 400ms. **C.** Ondansetron had no significant effect on the correlation of variance of APD₈₀ in normal ventricles. **D.** The Δ APD₈₀ shows that ondansetron prolonged the APD₈₀ 1-3% in normal ventricles. Δ APD = APD₈₀ after ondansetron - APD₈₀ at baseline. *P < 0.05.

Figure 4.

Optical mapping of pacing-induced TdP. **A.** Ondansetron significantly prolonged the APD at a PCL of 300 ms. **B.** S1/S2 pacing protocol induced TdP after ondansetron administration. **C.** At baseline, there was no spontaneous or S1/S2 pacing-induced TdP. After ondansetron infusion, either spontaneous, pacing-induced TdP or EAD were observed in 4 ventricles. **D.** APD₈₀ of the S1 and S2 show an increase in APD heterogeneity prior to TdP initiation. A reentrant activation map is shown with the first beat after the S2, which correlates to a phase singularity. The pacing site was located at the left ventricular apex (∩).

Figure 5.

Effect of ondansetron on the maximal slope of APD restitution (APDR) and 2:2 alternans in failing ventricles. **A.** APDR curves and maximal slopes of the curves sampled at basal and apical areas of one representative failing ventricle. **B.** Summary data shows that ondansetron significantly increased the maximal slope of APDR, and the threshold of alternans (**C**) in failing ventricles. **D.** At baseline, no VF was inducible with burst pacing, however after ondansetron infusion, VF was induced in 5 of the 7 failing ventricles.

Figure 6.

Effect of 100 nM of ondansetron on I_{KAS} . **A.** APD₈₀ was significantly lengthened after ondansetron infusion in failing hearts, but apamin failed to lengthen APD₈₀ any further. **B.** Ondansetron significantly prolonged hypokalemic normal ventricles, but subsequent administration of apamin failed to further prolong APD₈₀ (c, d), and vice versa (e, f). All data was analyzed from RV or LV at a PCL of 300 ms.

Figure 7.

Ondansetron (Ondans) inhibits SK currents in isolated ventricular myocytes. *A*, heart failure rabbits. *left*: representative ramp currents in control (black), in the presence of 100 nM ondansetron (red), and after addition of 100 nM apamin (blue) in the continual presence of ondansetron. *A, middle*: current-voltage relationships for current inhibited by ondansetron and for current inhibited by both ondansetron and apamin for the same cell as on the *left*. *A, right*: summary of current-voltage relationships for current inhibited by ondansetron and for current inhibited by both ondansetron and apamin. Ondansetron-sensitive and (ondansetron + apamin)-sensitive currents are not significantly different ($p=0.2895$ at +40 mV; $p=0.3423$ at

+30 mV; $p=0.1814$ at +20 mV; $p=0.3701$ at +10 mV). Values are means $\pm$ SEM of 4 cells. B, heart failure rabbits. *left*: representative ramp currents in control (black), in the presence of 100 nM apamin (blue), and after addition of 100 nM ondansetron (red) in the continual presence of apamin. B, *middle*: current-voltage relationships for current inhibited by apamin and for current inhibited by cumulatively applied ondansetron for the same cell as on the *left*. B, *right*: summary of current-voltage relationships for current inhibited by apamin and for current inhibited by ondansetron in the continuing presence of apamin. Apamin-sensitive and (apamin+ondansetron)-sensitive currents are not significantly different ($p=0.8206$ at +40 mV; $p=0.9832$ at +30 mV; $p=0.8609$ at +20 mV; $p=0.6829$ at +10 mV). Values are means $\pm$ SEM of 5 cells. C, normal rabbit cardiomyocytes in hypokalemia. *left*: representative ramp currents in control (black), in the presence of 100 nM ondansetron (red), and after addition of 100 nM apamin (blue) in the continual presence of ondansetron. C, *middle*: current-voltage relationships for current inhibited by ondansetron and for current inhibited by both ondansetron and apamin for the same cell as on the *left*. C, *right*: summary of current-voltage relationships for current inhibited by ondansetron and for current inhibited by both ondansetron and apamin. Ondansetron-sensitive and (ondansetron+apamin)-sensitive currents are not significantly different ($p=0.4631$ at +40 mV; $p=0.1446$ at +30 mV; $p=0.3046$ at +20 mV; $p=0.5081$ at +10 mV). Values are means $\pm$ SEM of 5 cells. D, normal rabbit cardiomyocytes in hypokalemia. *left*: representative ramp currents in control (black), in the presence of 100 nM apamin (blue), and after addition of 100 nM ondansetron (red) in the continual presence of apamin. D, *middle*: current-voltage relationships for current inhibited by apamin and for current inhibited by cumulatively applied ondansetron for the same cell as on the *left*. D, *right*: summary of current-voltage relationships for current inhibited by apamin and for current inhibited by ondansetron in the continuing presence of apamin. Apamin-sensitive and (apamin+ondansetron)-sensitive currents are not significantly different ($p=0.8273$ at +40 mV; $p=0.9280$ at +30 mV; $p=0.9561$ at +20 mV; $p=0.8622$ at +10 mV). Values are means $\pm$ SEM of 4 cells.

Table 1 –

Echocardiographic Studies

	<i>Before Pacing</i>	<i>After Pacing</i>	<i>P value</i>
<i>LVEDD (mm)</i>	11.3±1.6	16.2±1.7	< 0.001
<i>LVESD (mm)</i>	7.6±0.7	14.2±1.9	< 0.001
<i>LVFS (%)</i>	35.1±6.3	12.9±3.1	< 0.001
<i>LVEF (%)</i>	72.0±7.1	33.6±6.0	< 0.001

Values are means ± SD. LVEDD – center ventricular end diastolic diameter; LVESD – center ventricular end systolic diameter; LVFS – center ventricular fractional shortening; LVEF – center ventricular ejection fraction