Effects of Exercise Training With and Without Ranolazine on Peak Oxygen Consumption, Daily Physical Activity, and Quality of Life in Patients With Chronic Stable Angina Pectoris

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Ranolazine reduces angina frequency and increases exercise capacity. We hypothesized that exercise training with ranolazine would allow subjects to train at greater intensities, resulting in greater improvements in exercise capacity, physical activity, and health-related quality of life (HRQOL). In a pilot study, subjects with chronic stable angina pectoris were randomized to ranolazine (n = 13) or placebo (n = 16). After a 2-week drug titration period, subjects participated in a 12-week exercise program. Peak VO_2, physical activity (via accelerometer), and HRQOL were assessed before and after training. After exercise training, peak VO_2increased twice as much with ranolazine (2.1 ± 3.4 ml/kg/min) as with placebo (0.9 ± 1.5) (both p <0.05). After exercise training, both groups significantly improved HRQOL score (p <0.05); however, the improvement with ranolazine (19 ± 21) was almost 50% greater than with placebo (13 ± 18). There was a significant decrease in maximal heart rate after training with ranolazine but not with placebo (group difference, p = 0.04). Oxygen pulse (peak VO_2/peak HR) increased in both groups after training; but, the increase was 4 times greater with ranolazine — resulting in a significant difference between groups (p = 0.044). In conclusion, patients with angina, the addition of ranolazine to an exercise program may improve aerobic fitness, physical activity, and HRQOL beyond the results of an exercise training program alone. Exercise training with ranolazine led to significantly greater increases in oxygen pulse, which is significantly correlated with stroke volume and is an independent predictor of mortality. **(Am J Cardiol 2019;124:655−660)**

Ranolazine has also been consistently shown to increase exercise capacity, time to exhaustion, and time to angina during a maximal exercise test.[1−5] Similarly, exercise training has many benefits for patients with chronic stable angina including: reductions in myocardial ischemia and angina attacks, improvements in functional capacity and beneficial long-term outcomes.[6] The primary purpose of the present study was to test whether exercise training plus ranolazine resulted in greater benefits than with exercise training alone. We hypothesized that taking ranolazine during exercise training would allow patients to exercise at greater intensities during training, and this would lead to greater training-induced improvements in peak oxygen consumption. As secondary outcomes, accelerometer data were used to examine whether exercise training plus ranolazine would lead to greater improvements in physical activity[7−10] and in a greater improvements in health-related quality of life (HRQOL), as assessed using the Seattle Angina Questionnaire (SAQ),[11] compared with exercise training without ranolazine.

Methods

The study was approved by the Duke University Investigational Review Board and registered at Clinicaltrials.gov (registry number: NCT01948310). This research was funded by a grant from Gilead, grant # IN-US-259-0171. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Participants with documented coronary artery disease diagnosis, stable chronic angina (>3 months) and frequent angina episodes (>3 times per week) were recruited from Durham, North Carolina and surrounding communities. The primary exclusion criteria were: physician scheduled revascularization within the next 6 months, class III or IV heart failure, class IV angina, angina occurring less than 10 beats above resting heart rate, myocardial infarction or coronary revascularization procedure within previous 2 months.

Upon consent, participants completed a maximal cardiopulmonary exercise test (CPET), one-week Actigraph

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accelerometer analysis,[8,10] and a SAQ.[11] Participants were randomized in a double-blind, placebo-controlled scheme stratified by gender into placebo or ranolazine. All measurements were taken at baseline, at the end of the 2 weeks drug/placebo ramp-up period followed by 12 weeks of exercise training while taking the drug/placebo twice each day. The Duke Investigational Drug Service managed the drug randomization scheme and prepared study drug; all study investigators, trainers, and assessors were blinded to drug allocation arm. The dose for both placebo and ranolazine groups was titrated from 1 to 2 pills twice a day, over a 2-week period. Ranolazine was increased from 500 mg twice a day during the first week to 1,000 mg twice a day in week 2. After drug/placebo titration an additional maximal exercise test, 1 week Actigraph accelerometer analysis, and SAQ were completed in order to account for physiological responses from the drug alone and to determine individualized angina threshold for exercise training. All participants completed a 12-week exercise intervention followed by a CPET, one-week Actigraph accelerometer, and SAQ.

The exercise intervention simulated a standard 12-week Phase II cardiac rehabilitation exercise program. All participants completed 30- to 45-min sessions of cardiovascular exercise, 3 times per week, at an intensity 6 to 12 beats below their individualized angina threshold as determined by the participant's second CPET. Participants completed a 5-min warm up and cool down in addition to individually tailored sessions structured around their individual angina severity, orthopedic, and other safety concerns. Treadmill was the primary mode of exercise, but additional equipment such as the New Step, elliptical, and Physiostep were utilized based on orthopedic need and interest. GARMIN (Olathe, Kansas) heart rate monitors were worn to continuously record heart rate, and to ensure participant compliance and safety. At the conclusion of each exercise session, heart rate data were downloaded and analyzed. During each session, participants were asked to self-report: the onset, duration, and severity of angina with a 4-point angina scale. All exercise sessions were completed at the Duke Cardiac and Pulmonary Rehabilitation Center during medically supervised hours and under the direct supervision of study staff exercise physiologists.

CPETs with a 12-lead electrocardiogram (ECG) and expired gas analysis were performed on a treadmill or stationary bike using a TrueMax 2400 Metabolic Cart (ParvoMedics; Sandy, Utah). Participants completed CPET testing at baseline, postrandomization and drug titration, and upon completion of the 12-week exercise intervention. The workload increased each minute until the participant chose to end the test or study personnel chose to end the test for safety concerns. Study staff monitored heart rate, 12-lead ECG, blood pressure, angina; the 2 highest, consecutive, 15-second readings from each test were averaged to determine absolute peak VO_2. Angina onset and severity in conjunction with heart rate was used to calculate the heart rate range for the duration of the exercise intervention. All testing sessions were completed at the Duke Center for Living under medical supervision and direct oversight by study staff exercise physiologists.

Multiple variables were derived from the exercise tests: including maximal heart rate (MHR), peak oxygen consumption, and peak oxygen pulse (oxygen pulse = oxygen consumption (ml/min)/heart rate [HR] (beats/min)), angina threshold (as a % of MHR). Oxygen pulse reflects the amount of oxygen consumed (or extracted from the blood) per heart beat[12–14] and when oxygen extraction is unchanged, oxygen pulse becomes a surrogate for stroke volume. This is based on the Fick equation where oxygen consumption = cardiac output (stroke volume × HR) × arterio-mixed venous oxygen difference (a-VO_2). When peak arterio-venous oxygen difference is the same (research suggests it does not change after exercise training[12]) and peak oxygen consumption is the same or increasing, a decrease in MHR must result in an increase in stroke volume and oxygen pulse in order to maintain cardiac output and peak oxygen consumption. However, there are important caveats as using oxygen pulse as a surrogate for stroke volume depends on 3 assumptions − no anemia, no hypoxemia, and no intracardiac or pulmonary shunts.

Analysis of covariance (with adjustment for baseline values) was used to test for differences in groups (Statview, Cary, North Carolina). Paired *t* tests were performed to determine significant changes within groups for the 2-week drug run-in period and for the complete 14-week study period. A p value of ≤ 0.05 was considered significant. Effect sizes were also calculated for the change scores. As this was a pilot study, a power calculator was used to estimate the number of subjects needed to test the primary outcome of change in peak VO_2.

Results

In total, 57 participants signed the informed consent, 38 met the final inclusion criteria of experiencing exertional angina during baseline CPET and were recruited for this study. One dropped out before randomization. Of the 37 randomized, 29 finished. Three dropped out of the placebo group and 5 dropped out of the ranolazine group. Two subjects reported dizziness after starting (both in the drug group); 1 physician wanted their patient to be on Ranolazine; 2 had new cardiac events (both in placebo); 2 changed their mind (both on drug, neither said why); and finally, 1 dropped out due to the expected time commitment (this subject was in placebo group). However, as this is a very small study, and based on the above varied reasons for dropping out, it is difficult to make any firm conclusions as to how these dropout rates would have affected the outcomes.

Baseline characteristics and medications taken are shown in Table 1. Adherence was similar for both groups (Placebo group − 88.6% ± 9.7%; Ranolazine group − 82.6% ± 16.0%). Table 2 shows maximal exercise test and accelerometer outcome data at baseline, 2 weeks and 14 weeks. In addition, change scores, p values, and effect sizes are included in Table 2. There were no baseline differences between groups for any variable in Table 2.

Neither group exhibited significant differences when compared with baseline in maximal oxygen consumption or time to exhaustion at 2 weeks. Although both groups significantly improved relative VO_2 (ml/kg/min) from baseline to postintervention (14 week) assessment, *the Ranolazine group improved* more than twice as much. At 14 weeks, the

Table 1
Baseline characteristics by study group

	Placebo (n = 16)	Ranolazine (n = 13)
Age (yrs)	69.2 (8.3)	67.4 (11.2)
Women/men	5 / 11	5 / 8
Black/white	5 / 11	4 / 9
BMI (kg/m^2)	32.1 (6.3)	32.3 (3.9)
Peak oxygen consumption (cardiovascular fitness; ml/kg/min)	15.7 (3.5)	16.5 (3.1)
Aspirin	13 (87%)	11 (79%)
ACE-I	4 (27%)	3 (21%)
Beta blockers	11 (73%)	10 (71%)
Calcium-channel blockers	5 (22%)	3 (21%)
Long-acting nitrates	9 (60%)	8 (57%)
Statins	15 (100%)	14 (100%)
Diuretics	3 (20%)	9 (64%)
Antidiabetic meds	6 (40%)	7 (50%)
Myocardial Infarction	7 (47%)	4 (29%)
Congestive heart failure (I or II)	3 (20%)	1 (7%)
Coronary artery bypass graft	9 (60%)	4 (29%)
Stent	8 (53%)	5 (36%)

Values are means (SD) unless otherwise indicated.
ACE-1 = angiotension-converting enzyme inhibitor.

placebo group significantly improved time to exhaustion during the maximal exercise test by 87.5 seconds ($p = 0.0001$) compared with baseline (0 week). Although the ranolazine group improved time to exhaustion by 54.3 seconds at 14 weeks, this merely trended ($p = 0.06$) toward significance. MHR decreased significantly in the ranolazine group at 2 and 14 weeks compared with baseline, whereas there was no change in MHR in the placebo group; this represented a significant difference between groups. In the ranolazine group the significant decrease in MHR combined with the increase in peak oxygen consumption resulted in an increase in O_2 pulse (amount of oxygen extracted per heart beat). Although both groups experienced significantly increased O_2 pulse after 14 weeks, the increase was 3 times greater and was statistically significant in the ranolazine compared with the placebo group ($p = 0.007$).

Importantly, we found that angina threshold when expressed as % of MHR (Table 2), or % of peak VO_2 (data not shown) increased from week 0 to week 2 in the ranolazine group but decreased in the placebo group. These changes were not significant and there were no group differences. However, the direction of these responses support the hypotheses that ranoloazine allowed subjects to exercise at a slightly higher intensity from the very start of exercise training. At 14 weeks several of the subjects in both groups no longer reported angina during the maximal exercise test and so we were unable to evaluate this at end of training.

Physical activity, nonexercise physical activity, and sedentary time were tracked via accelerometers. As expected, the measurements for total physical activity and nonexercise physical activity were identical in the 2 groups at 0 and 2 weeks. When compared with baseline, ranolazine increased ($p < 0.05$) total physical activity at 14 weeks. Although, total physical activity increased similarly in the placebo group, due to greater variability in response, this was not significant. There was no significant change in nonexercise physical activity at 2 or 14 weeks in either group. Importantly, this finding indicates that even with the addition of a vigorous intensity aerobic exercise program in chronic angina patients, there was no indication that there was a decrease in other physical activity in either group.

SAQ outcome data at baseline, 2 weeks and 14 weeks are shown in Table 3. The main variable of interest for this protocol was HRQOL; however, all f domains are presented in Table 3. The ranolazine group reported a highly significant improvement in HRQOL score after only 2 weeks ($p = 0.0007$). This improvement in the ranolazine group was significantly greater than the change experienced by the placebo group ($p = 0.044$). By the end of the 14-week study, both groups experienced significant improvements in HRQOL scores, but the improvement with ranolazine was approximately 50% greater than that achieved with exercise alone.

Discussion

In this study, we observed that compared with exercise training with placebo, training with ranolazine resulted in more than twice as great an improvement in peak oxygen consumption and a reduction in angina threshold. These data support our hypothesis that the combined effects of taking ranolazine and exercise training would lead to greater improvements in aerobic exercise capacity than with exercise training alone. Importantly, the greater increase in oxygen consumption, combined with the decrease in MHR experienced by the ranolazine group, resulted in a significant increase in oxygen pulse an increase that was 3 times greater and statistically superior to the increase in oxygen pulse experienced by the placebo group. These data taken together with the strong, consistent, and highly significant findings of reduced rate pressure product reported by others,[21] strongly suggest that one of ranolazine's mechanisms of action may be to reduce myocardial oxygen consumption with each increase in workload during a graded treadmill test. Finally, perhaps due to these favorable effects on cardiac work during exercise and the resultant increase in angina-work threshold, ranolazine administration resulted in a nearly 50% greater increase in the SAQ Quality of Life Index. These data suggest that a larger follow-up study of ranolazine plus exercise training is indicated to more definitively test these primary and secondary hypotheses.

To our knowledge, this is the first study to measure peak VO_2, as previous studies have instead reported treadmill time to exhaustion. The value of cardiorespiratory fitness with peak oxygen consumption for predicting morbidity and mortality has been repeatedly established in cross-sectional[14–18] and longitudinal[19] studies. However, as indicated with our intriguing results for O_2-pulse, measurement of gas exchange during an exercise test can provide additional mechanistic information informing hypotheses about drug effects. As expected, over the course of the exercise training study, both groups experienced significant improvements in peak VO_2. Consistent with our motivating mechanistic hypothesis, ranolazine combined with exercise increased peak VO_2 by approximately twice that experienced in the placebo plus exercise group. However, there were no

Table 2
Maximal exercise test and accelerometer outcome data at baseline, 2 and 14 weeks, and change scores

				Change scores					
	†0 week	2 weeks	14 weeks	2-0 weeks	p Value	Effect size	14 weeks-0 week	p Value	Effect size
Angina threshold (% of MHR)									
Placebo	87 (9)	86 (10)	-	−0.93 (7)	ns	0.14	-	-	-
Ranolazine	90 (8)	92 (4)	-	1.53 (8)	ns	0.19	-	-	-
Peak VO_2 (ml/kg/min)									
Placebo	15.7 (3.5)	15.7 (3.3)	16.7 (4.2)	0.03 (1.2)	ns	0.03	0.9 (1.5)	0.03	0.60
Ranolazine	16.5 (3.1)	16.9 (3.8)	18.4 (5.5)	0.38 (1.9)	ns	0.20	2.1 (3.4)	0.005	0.62
Peak VO_2 (L/min)									
Placebo	1.42 (0.5)	1.43 (0.5)	1.51 (0.5)	0.01 (0.12)	ns	0.08	0.08 (0.13)	0.03	0.62
Ranolazine	1.54 (0.4)	1.58 (0.5)	1.67 (0.6)	0.04 (0.18)	ns	0.22	0.146 (0.22)	0.03	0.66
Time to exhaustion (s)									
Placebo	376 (103)	383 (89)	463 (141)	7.3 (42)	ns	0.18	87.5 (68.1)	0.0001	1.28
Ranolazine	401 (134)	403 (121)	456 (148)	1.8 (43)	ns	0.04	54.3 (92.6)	0.06	0.59
Max heart rate (bpm)									
Placebo	124 (18)	123 (19)	124 (20)	−0.47 (9) *	ns	0.05	0.53 (9) *	ns	0.06
Ranolazine	131 (19)	123 (15)	121 (17)	−8.7 (11)	0.013	0.79	−10.5 (15)	0.025	0.70
Oxygen pulse (ml/beat)									
Placebo	11.8 (3)	11.4 (3)	12.4 (3)	0.06 (0.8)	ns	0.08	0.56 (0.8) ***	0.028	0.70
Ranolazine	11.5 (4)	12.7 (4)	13.4 (4)	0.73 (1.4)	0.085	0.52	1.87 (1.9)	0.003	0.98
Total physical activity (kJ/h)									
Placebo	117 (64)	119 (66)	139 (72)	2.0 (39)	ns	0.05	22.2 (54.2)	0.13	0.41
Ranolazine	123 (80)	116 (78)	148 (99)	−7.6 (29)	ns	0.26	24.3 (29.9)	0.013	0.81
Nonexercise PA (kJ/h)									
Placebo	117 (64)	119 (66)	116 (61)	2.0 (39)	ns	0.05	−0.37 (51.7)	ns	0.01
Ranolazine	123 (80)	116 (78)	129 (86)	−7.6 (29)	ns	0.26	6.02 (21.3)	ns	0.28
Sedentary time (min)									
Placebo	612 (164)	556 (129)	629 (110)	−56.3 (214)	ns	0.26	17.1 (182)	ns	0.09
Ranolazine	607 (102)	640 (128)	602 (99)	33.4 (38)	0.008	0.88	−4.6 (72.8)	ns	0.06
Steps									
Placebo	4,211 (2,335)	3,783 (1,775)	5,404 (2,531)	−428 (1,481)	ns	0.29	1,193 (1,073)	0.0007	1.11
Ranolazine	4025 (1,919)	3779 (1,606)	5344 (3,130)	−246 (907)	ns	0.27	1,319 (1,913)	0.03	0.69

Data are means (SD).

For the variable "Angina Threshold (% MHR - max heart rate)", data are only presented at 0 and 2 weeks due to the large number of subjects who did not experience during the exercise tests at 14 weeks.

† From 0 weeks to 2 weeks both the drug ranolazine and the placebo were titrated up to 2 pills twice a day (final does for ranolazine was 1,000 mg twice per day). From 2 weeks to 14 weeks all subjects took ranolazine or placebo and participated in exercise training 30 to 45 minutes a session, 3 sessions per week. $p < 0.05$ is considered significant.

* Indicates a trend ($p < 0.10$) toward a significant difference between the placebo and ranolazine groups.

*** indicates a significant ($p < 0.01$) difference between placebo and ranolazine groups.

Table 3
Seattle Angina Questionnaire outcome data at baseline 2 and 14 weeks and change scores

				Change scores					
	*0 weeks	2 weeks	14 weeks	2-0 weeks	p Value	Effect size	14 weeks-0 week	p Value	Effect size
QoL									
Placebo	57 (16)	60 (23)	70 (21)	2.6 (17)	ns	0.15	13.0 (18)	0.012	0.71
Ranolazine	51 (25)	67 (22)	71 (22)	15.4 (12)	0.0007	1.26	19.2 (21)	0.007	0.90
PhysLim									
Placebo	59 (11)	62 (15)	68 (16)	3.1 (15)	ns	0.21	9.5 (15)	0.02	0.63
Ranolazine	68 (19)	65 (20)	75 (21)	−3.0 (15)	ns	0.20	6.5 (24)	ns	0.27
AngFreq									
Placebo	60 (17)	66 (18)	72 (21)	5.6 (10)	0.03	0.58	11.9 (20)	0.03	0.59
Ranolazine	65 (24)	70 (28)	79 (16)	4.6 (22)	ns	0.21	13.1 (18)	0.02	0.73
AngStab									
Placebo	59 (156)	59 (18)	77 (23)	0.0 (20)	–	0.00	17.2 (29)	0.03	0.60
Ranolazine	56 (33)	58 (24)	69 (27)	1.9 (28)	ns	0.07	13.5 (36)	0.21	0.37
TreatSat									
Placebo	84 (16)	85 (14)	87 (11)	0.8 (9)	ns	0.09	3.1 (13)	ns	0.23
Ranolazine	89 (11)	94 (8)	88 (14)	5.3 (8)	0.03	0.66	−1.0 (13)	ns	0.08

Data are means (SD). $p < 0.05$ is considered significant.

* From 0 weeks to 2 weeks both the drug ranolazine and the placebo were titrated up to 2 pills twice a day (final does for ranolazine was 1,000 mg twice per day). From 2 weeks to 14 weeks all subjects took ranolazine or placebo and participated in exercise training 30 to 45 minutes a session, 3 sessions per week.

significant differences between the ranolazine and placebo group for peak oxygen consumption or time to exhaustion. Using data from each group, (alpha of 0.05 and a power of 0.80), power calculations reveal that 71 finishers per group would be required to adequately test our primary hypotheses.

Ranolazine administration resulted in a highly significant improvement in HRQOL - SAQ during the 2-week drug run-in phase (before training) (Table 2). By the end of the 12 weeks of exercise training, both groups had statistically and clinically meaningful improvements in HRQOL. Although the ranolazine plus training group experienced a nearly 50% greater total improvement in HRQOL score compared with the exercise plus placebo group, this difference between groups was not significant.

Accelerometer data show exercise training plus ranolazine increased nonexercise physical activity, whereas the change score for the placebo group was slightly negative. Interestingly and unexpectedly, ranolazine significantly increased sedentary time ($p = 0.008$) during the 2 week run-in phase. These findings are supportive of those by Birkeland et al,[20] who reported a significantly decreased stepcount over the 2-week placebo-controlled, randomized, crossover trial on 30 subjects. By the end of the present study, daily sedentary time was no different from baseline in either group. This is important as it is often suggested that starting an exercise program will result only in a compensatory decrease in off-exercise physical activity. We and others have shown this hypothesis to be in error in several study populations.[7,8,10] These findings can now be extended to include patients with chronic stable angina pectoris.

Importantly the decreased MHR combined with increased in peak oxygen consumption in the ranolazine group resulted in a trend ($p = 0.085$) toward an increase in oxygen pulse—the amount of oxygen consumed by the body with each cardiac contraction. Consequently, we can conclude that peak oxygen extraction (arterial minus venous oxygen content) and/or stroke volume is increased as result of the ranolazine.

Based on the Fick equation (see Methods), the increased oxygen pulse is likely a reflection of an increased stroke volume as studies consistently show no change in oxygen extraction with exercise training.[12] This is important for understanding the synergistic effects of exercise and ranolazine on whole-body work capacity—a mechanism of ranolazine action worthy of further exploration. Important caveats to using oxygen pulse as a surrogate for stroke volume include: no anemia, no hypoxemia, and no intracardiac or pulmonary shunts.

The reduction in MHR is supported by other studies and suggests that ranolazine may decrease cardiac work with exercise, which may be one mechanism whereby ranolazine results in greater work capacity while taking the drug in those with angina-limiting exercise capacity.[4] Recently Stone et al,[21] reported clear and consistent decreases in maximal and submaximal HR that were more evident with greater doses of ranolazine and with increasing levels of exertion during the graded maximal exercise test. Additionally, they reported reduced systolic blood pressures throughout the graded treadmill test, which was more pronounced with greater doses of ranolazine. These reductions in blood pressures and heart rates result in reductions in rate pressure products, reflecting reduced cardiac workloads at any given cardiac output.[22,23] By itself, the reduced pressure product would almost certainly reduce ischemia and angina at any given work rate. Importantly, Stone et al was a large study using a crossover design with 191 subjects which leads to significant confidence in this finding.

A major limitation of this study was the small sample size. Although the unique measurements of oxygen consumption and accelerometer data are strengths, it will require a much larger subject number to more definitively study the effect of combining ranolazine and exercise training on these measurements.

In summary, compared with exercise training alone, exercise training with ranolazine resulted in greater increases in angina threshold, oxygen pulse, and in peak oxygen consumption. These data support the hypothesis that the combined effects of ranolazine and exercise training lead to greater improvements in aerobic exercise capacity than observed with exercise training alone. Perhaps due to the favorable effects on cardiac work during exercise and the resultant increase in angina-work threshold, ranolazine administration resulted in a nearly 50% greater increase in the SAQ Quality of Life Index. As this was a small study, most of these findings were not statistically significant; therefore these data suggest that a larger follow-up study is indicated to more definitively test these hypotheses.

Disclosures

The authors have no conflicts of interest to disclose.

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