Original Research

Effects of Ranolazine on Left Ventricular Diastolic and Systolic Function in Patients with Chronic Coronary Disease and Stable Angina

Dimitrios Babalis, Vlassis Tritakis, Georgios Floros, Aggeliki Mouzarou, Nikolaos Kafkas, Konstantina Bampali, Georgios Mertzanos

Cardiology Department, KAT General Hospital of Athens, Greece

Key words: **Coronary disease, ranolazine, ventricular function.**

Introduction: The present study examined the effect of ranolazine, which acts via the mechanism of selective inhibition of late I_{Na+}, on parameters of left ventricular systolic and diastolic function in patients suffering from angiographically confirmed chronic coronary artery disease, presenting with chronic stable angina.

Methods: We studied 40 patients (age 67 ± 9 years; 30 men, 10 women) with chronic coronary artery disease who reported angina symptoms on optimal medication and who were not suitable for invasive treatment. Patients were randomized to the ranolazine group (group A, 20 patients taking oral ranolazine 500 mg bid for 3 months) and the control group (group B, 20 patients who did not receive the drug). Left ventricular systolic and diastolic function was assessed echocardiographically at baseline and after the end of the three-month treatment period. Left ventricular ejection fraction by the modified Simpson's method, E and A left ventricular filling velocities, E/A ratio, deceleration time (DT) of E, isovolumic relaxation time (IVRT), E´ and A´ waves, and the E/E´ ratio were measured using 2-dimensional echocardiography, Doppler and tissue Doppler imaging (TDI).

Results: Group A patients demonstrated a clear improvement of their initial angina symptoms. There were no adverse effects from ranolazine requiring withdrawal from the study. There was no statistically significant change in left ventricular systolic function in either group. A statistically significant change was seen in indexes of diastolic function measured using both conventional Doppler and TDI in Group A patients compared with Group B patients after three months' ranolazine treatment period. The changes in left ventricular diastolic function indexes in Group A patients were as follows: E 0.58 ± 0.11 vs. 0.76 ± 0.12 m/s, $p<0.001$; A 0.71 ± 0.22 vs. 0.83 ± 0.19 m/s, $p<0.001$; E/A 0.81 ± 0.14 vs. 0.97 ± 0.17, $p<0.005$; E´ 5.4 ± 0.7 vs. 6.8 ± 0.9 cm/s, $p<0.005$; A´ 7.2 ± 0.8 vs. 8.3 ± 1.1 cm/s, $p<0.005$; E/E´ 10.7 ± 1.1 vs. 11.1 ± 0.8, p=ns; DT 251 ± 14 vs. 226 ± 17 ms, $p<0.004$; IVRT 95 ± 11 vs. 74 ± 9 ms, $p<0.001$. Systolic function did not change: EF 46.3 ± 3.4 vs. 46.7 ± 2.7%, p: ns.

Conclusions: The use of ranolazine in patients suffering from chronic coronary artery disease has a favorable impact on diastolic function parameters. Accordingly, a clinical benefit could be observed due to an improvement in patients' symptoms.

Manuscript received:
April 2, 2014;
Accepted:
November 3, 2014.

Address:
Dimitrios Babalis

Department of Cardiology
KAT General Hospital of Athens
2 Nikis St.
14561 Kifissia, Greece
babalisd@yahoo.gr

Coronary artery disease is one of the most prevalent diseases in the Western world and angina is its most important symptom. It has been estimated that angina affects 15,000-40,000/1,000,000 individuals in the US and in most European countries.[1,2] The management of patients with coronary disease and chronic stable angina is commonly based on lifestyle changes (e.g. healthier diet), pharmacological interventions, and invasive procedures such as percutaneous angioplasty or surgical revascularization.[3] However, the ARTS study demonstrated

that, at a 3-year follow up, 78% of the patients treated with percutaneous angioplasty and 65% of those who had undergone bypass surgery for multivessel coronary disease were still on treatment with anti-angina drugs.[4] The introduction of novel medications into the pharmaceutical armamentarium for the treatment of angina is therefore urgently needed, with the aim of improving symptoms and reducing the hospitalizations of patients with coronary disease.

Among these medications, ranolazine has been supposed to play a major role.[5] However, the specific effects of ranolazine on left ventricular diastolic and systolic function have not been adequately studied.[6] This randomized study specifically investigated the effects of ranolazine on left ventricular systolic and diastolic function in patients with chronic coronary artery disease and stable angina.

Patients and methods

Study setting and design

This was a randomized placebo-controlled phase II study, conducted at the cardiology department of KAT General Hospital of Athens from December 2010 to June 2011. The study protocol was approved by the local Ethics Committee, and the study was conducted in accordance with the Helsinki Declaration. All patients signed an informed consent form before inclusion.

Patients

Typical angina consists of substernal chest discomfort of characteristic quality and duration that is provoked by exertion or emotional stress and relieved by rest and/or nitrates within minutes. The term "refractory angina" is defined as a chronic condition caused by clinically established reversible myocardial ischemia in the presence of coronary artery disease, which cannot be adequately controlled by a combination of medical therapy, angioplasty or coronary artery bypass graft.[7]

Adult patients with coronary disease (coronary stenosis >70% in one or more vessels, as documented by angiography) and symptoms of stable angina, despite optimized anti-angina treatment, who were not suitable for further invasive treatment, were eligible for this study. Exclusion criteria were the following: severe ischemic heart failure (New York Heart Association class [NYHA] III or IV); unstable angina; recent (<1 month) myocardial infarction; and ongoing treatment with drugs that might prolong the QT interval on the ECG. It is worth mentioning that 2 patients of group A and 4 from group B were not eligible for revascularization because of complicated coronary anatomy or lack of grafts.

Study procedures and assessments

Patients were randomly assigned, in a 1:1 ratio, to either optimized medical treatment plus ranolazine (500 mg tablets bid) or antianginal medical treatment without ranolazine, for a total period of 3 months. An increase in exercise capacity and duration, and retardation of the appearance of anginal symptoms were some of the benchmarks of our study. There was frequent contact between patients and the study physicians for monitoring of their clinical status.

Left ventricular systolic and diastolic function was assessed at baseline and at the end of the study period. All measurements were performed in the specialized ultrasound laboratory of the institution where the study was conducted, by the same trained physician, using an iE33 device (Philips, US). Data were analyzed using QLAB software (Philips, US).

Left ventricular ejection fraction was assessed according to the modified Simpson's rule, while E and A left ventricular filling velocities, E/A ratio, E-wave deceleration time (DT), isovolumic relaxation time (IVRT), E´ and A´ waves, and the ratio E/E´ were evaluated using two-dimensional echocardiography, Doppler, and tissue Doppler imaging (TDI).

Safety evaluations were also performed, and the correlation between treatment-emergent adverse events and the study medication was assessed by the investigators.

Data analysis

All data were analyzed by descriptive statistics. Comparisons between different time points and study groups were performed using Student's t test. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 13.0 software (SPSS, Chicago, Il, USA).

Results

Patient population

In total, 40 patients were included in the study (20 patients in each group). Table 1 depicts their baseline characteristics. Thirty patients (the majority) were men and the mean age was 69 ± 7 years.

Table 1. Baseline characteristics.

	Ranolazine (n=20)	No medication (n=20)
Age (years)	66 ± 9	67 ± 4
Sex (men)	14	16
SMO	13	12
DM	7	6
HYP	16	16
FH	9	8
DYSL	14	16
NITR	19	18
ACEI	14	15
ARBs	6	5
ANTIP	20	20
HYPOL	19	20
CA ANT	4	5
B BLOC	19	18
PCI	14	15
CABG	6	5
CHOL (mg/dL)	198 ± 14	196 ± 11
TG (mg/dL)	132 ± 19	138 ± 27
HDL (mg/dL)	39 ± 4	36 ± 9
LDL (mg/dL)	119 ± 11	117 ± 22

SMO – smoking habits; DM – diabetes mellitus; HYP – hypertension; FH – family history of coronary artery disease; DYSL – dyslipidemia; NITR – nitrates; ACEI – angiotensin-converting enzyme inhibitors; ARBs – angiotensin receptor blockers; ANTIP – antiplatelets; HYPOL – hypolipidemics; CA ANT – calcium antagonists; B BLOC – β-blockers; PCI – percutaneous coronary intervention on culprit damage; CABG – coronary artery bypass graft; CHOL – cholesterol; TG – triglycerides; HDL – high-density lipoprotein; LDL – low-density lipoprotein.

Left ventricular systolic and diastolic function

Table 2 reports the values of the left ventricular function parameters during the study period. Most parameters improved compared with baseline values in the ranolazine-treated group, whereas no improvement was seen in the control group. At study end, ranolazine-treated patients had better diastolic function parameters than those in the control group, as assessed by both conventional Doppler and TDI (Table 2). Most patients in group A showed an improvement in rehospitalization frequency and exercise capacity, while no patient withdrew from the study because of ranolazine-related adverse reactions. No significant improvement in CCS classification or exercise capacity occurred in the group B patients.

Safety

No drug-related adverse events, such as QT interval prolongation, dizziness, nausea, dyspnea, headache, constipation, etc., were reported.

Discussion

A major problem in clinical cardiology is the management of patients with chronic coronary artery disease and stable angina: although they have undergone invasive treatment in the past (angioplasty or bypass), stable angina symptoms persist or reappear within a reasonable time period, while they are also considered ineligible for further invasive treatment. Another major issue encountered with coronary patients is left ventricular diastolic dysfunction, which may coexist even with normal left ventricular systolic performance and, if it progresses, may cause symptoms of heart failure. Furthermore, substantial differences in demographics, clinical profiles, and treatment in patients with stable coronary artery disease were observed in cohorts between populations in Western

Table 2. Left ventricular function parameters at baseline and at study end.

	Baseline		3 months		p-value for intergroup comparison at study end
	Ranolazine (n=20)	No medication (n=20)	Ranolazine (n=20)	No medication (n=20)	
E (m/s)	0.58 ± 0.11	0.56 ± 0.19	0.76 ± 0.12*	0.56 ± 0.14	<0.001
A (m/s)	0.71 ± 0.22	0.68 ± 0.19	0.83 ± 0.19*	0.71 ± 0.16	<0.001
E/A	0.81 ± 0.14	0.79 ± 0.17	0.97 ± 0.17†	0.78 ± 0.19	<0.001
E´ (cm/s)	5.4 ± 0.7	5.2 ± 0.9	6.8 ± 0.9†	5.2 ± 0.95	<0.001
A´ (cm/s)	7.2 ± 0.8	7.1 ± 0.6	8.3 ± 1.1†	7.0 ± 0.92	<0.001
E/E´	10.7 ± 1.1	10.4 ± 0.9	11.1 ± 0.8	10.7 ± 1.2	NS
DT (ms)	251 ± 14	252 ± 12	226 ± 17†	250 ± 12	<0.001
IVRT (ms)	95 ± 11	94 ± 8	74 ± 9*	92 ± 16	<0.001
EF (%)	46.3 ± 3.4	44.1 ± 2.9	46.7 ± 2.7	44.6 ± 2.1	NS

*p<0.001 vs. baseline; †p<0.005 vs. baseline. E – maximum velocity of early diastolic transmitral filling; A – end-diastolic filling due to atrial contraction; E´ – early diastolic mitral annular velocity; A´ – late diastolic mitral annular velocity; DT – E-wave deceleration time; IVRT – isovolumic relaxation time; EF – left ventricular ejection fraction.

Europe.[8] Therefore, the medical management of stable angina is of great significance.[9]

Ranolazine is a novel antianginal agent that inhibits the late Na^+ current in myocardial cells and ameliorates the disrupted sodium and calcium homeostasis.[5] It is metabolized in the liver and the intestine.[10] Ranolazine prevents the pathological intracellular Ca^{++} accumulation that leads to ischemia and heart failure. Under normal conditions, the function of the myocardial cell is characterized by a balance between the influx and efflux of sodium ions. In pathological conditions, such as myocardial ischemia, ventricular hypertrophy and heart failure, there is a prolonged late Na current (I_{Na}) during phase 2 of the cardiac action potential.[11]

Several studies, such as MARISA, CARISA and ERICA, have demonstrated that ranolazine significantly reduces angina frequency and improves exercise performance in coronary patients.[12-14] Therefore, the therapeutic value of this agent for the reduction of the frequency of stable angina attacks and the improvement of the patient's exercise capacity is considered unquestionable. On the other hand, according to the MERLIN-TIMI 36 trial, although ranolazine had no effect on cardiovascular death or myocardial infarction in patients with a non-ST-elevation acute coronary syndrome, its antianginal effect was confirmed, with a significant reduction in recurrent ischemia.

However, the effects of ranolazine on parameters of left ventricular systolic and diastolic function in patients with chronic coronary artery disease and stable angina have, to our knowledge, never been investigated in a randomized trial: only a small, uncontrolled trial had previously addressed this issue, demonstrating improvement of left ventricular diastolic and systolic function following the administration of ranolazine in patients with stable angina.[15]

Although conducted in an overall limited number of patients, our study, with its randomized design, shows that ranolazine 500 mg bid in chronic coronary patients improves parameters of left ventricular diastolic function, whereas no effect on left ventricular systolic function was demonstrated. Moreover, ranolazine-treated patients showed an improvement in the severity of stable angina. Notably, these effects were achieved without any drug-related adverse events.

The purpose of the study was primarily the echocardiographic evaluation of left ventricular function and secondarily the improvement of the patients' clinical outcome. For this reason, we proceeded to the administration of the medicine (at the maximum dose of 500 mg bid.) for the management of anginal complaints. The improvements in anginal symptoms and exercise capacity were promising in those patients who were treated with ranolazine, even during this three-month period with a dose of 500 mg bid; thus, it was not necessary to titrate the dose up to 750 mg.

This study is not without its limitations: they include the limited number of patients, the single-center setting, and the lack of an active comparator. Despite these limitations, it is possible to conclude that ranolazine improves the clinical symptoms and the daily living activities, as mentioned above, in patients with coronary heart disease who suffer chronic stable angina. Further research on ranolazine involving a larger number of patients is warranted to provide additional evidence about the role of this drug in the treatment of patients with chronic coronary artery disease and stable angina.

Acknowledgments

The authors declare that they have no conflict of interest. Editorial assistance for the preparation of this manuscript was provided by Luca Giacomelli, PhD, on behalf of Content Ed Net; this assistance was funded by Menarini International.

References

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009; 119: 480-486.
2. Fox K, Garcia MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J. 2006; 27: 1341-1381.
3. Michalsen A, Knoblauch NT, Lehmann N, et al. Effects of lifestyle modification on the progression of coronary atherosclerosis, autonomic function, and angina—the role of GNB3 C825T polymorphism. Am Heart J. 2006; 151: 870-877.
4. van Domburg RT, Daemen J, Pedersen SS, et al. Short- and long- term health related quality-of-life and anginal status after randomisation to coronary stenting versus bypass surgery for the treatment of multivessel disease: results of the Arterial Revascularisation Therapy Study (ARTS). EuroIntervention. 2008; 3: 506-511.
5. Kloner RA, Hines ME, Geunes-Boyer S. Efficacy and safety of ranolazine in patients with chronic stable angina. Postgrad Med. 2013; 125: 43-52.
6. Lovelock JD, Monasky MM, Jeong EM, et al. Ranolazine improves cardiac diastolic dysfunction through modulation of myofilament calcium sensitivity. Circ Res. 2012; 110: 841-850.
7. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery dis-

ease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013; 34: 2949-3003.
8. Sbarouni E, Voudris V, Georgiadou P, et al. Clinical presentation and management of stable coronary artery disease: insights from the international prospective CLARIFY registry - results from the Greek national cohort. Hellenic J Cardiol. 2014; 55: 442-447.
9. Andrikopoulos G, Parissis J, Filippatos G, et al. Medical management of stable angina. Hellenic J Cardiol. 2014; 55: 272-280.
10. Penman AD, Eadie J, Herron WJ, Reilly MA, Rush WR, Liu Y. The characterization of the metabolites of ranolazine in man by liquid chromatography mass spectrometry. Rapid Commun Mass Spectrom. 1995; 9: 1418-1430.
11. Bers DM, Barry WH, Despa S. Intracellular Na+ regulation in cardiac myocytes. Cardiovasc Res. 2003; 57: 897-912.
12. Chaitman BR, Skettino SL, Parker JO, et al; MARISA Investigators. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol. 2004; 43: 1375-1382.
13. Chaitman BR, Pepine CJ, Parker JO, et al; Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA. 2004; 291: 309-316.
14. Stone PH, Gratsiansky NA, Blokhin A, Huang IZ, Meng L; ERICA Investigators. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. J Am Coll Cardiol. 2006; 48: 566-575.
15. Figueredo VM, Pressman GS, Romero-Corral A, Murdock E, Holderbach P, Morris DL. Improvement in left ventricular systolic and diastolic performance during ranolazine treatment in patients with stable angina. J Cardiovasc Pharmacol Ther. 2011; 16: 168-172.