Original Article

Effects of Doxycycline on Left Ventricular Remodeling in Patients With Acute Anterior Myocardial Infarction Uundergoing Primary Angioplasty: A Randomized Clinical Trial

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ABSTRACT

Background: Inflammatory mechanisms can cause left ventricular (LV) remodeling. These mechanisms include increased matrix metalloproteinases and the tissue inhibitors of metalloproteinases. Doxycycline is an antibiotic (macrolide) and a broad inhibitor of matrix metalloproteinases. This study evaluated the effects of early short-term doxycycline treatment on LV remodeling in patients suffering from ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Methods: In the present double-blinded randomized control trial, 68 post-MI patients who underwent primary PCI for STEMI were assigned to 2 groups, each consisting of 34 volunteers. Over a 7-day period, all these volunteers took 100 mg of Doxycycline twice a day. A placebo with the same order was prescribed for the control group. The cardiac function, the LV diameter, the left atrial diameter, and the LV torsion were measured at baseline and 40 days afterward.

Results: The mean age of the control and experimental groups was 53.7 years and 56.1 years, respectively. The averages of the left atrial volume (P = 0.03), the LV end-diastolic volume (P = 0.03), and the LV end-systolic volume (P = 0.01) in the experimental group rose less significantly than those in the control group. However, the LV torsion such as basal rotation (P = 0.03), apical rotation (P = 0.02), twist (P = 0.02), and torsion (P = 0.002) increased more substantially in the experimental group than in the control group.

Conclusions: Early administration of doxycycline attenuated LV remodeling measured by speckle-tracking echocardiography in our patients with anterior STEMI after primary PCI, vs. our control group subjects, who were on a placebo diet. ***(Iranian Heart Journal 2019; 20(4): 22-30)***

KEYWORDS: Left ventricular remodeling, ST-segment elevation, Torsion, Twist

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Received: January 15, 2019 **Accepted:** March 25, 2019

Myocardial infarction (MI) is one of the main causes of death in the world. ST-elevation myocardial infarction (STEMI) causes molecular, structural, and functional changes in the heart, termed "left ventricular (LV) remodeling". [1] LV remodeling is one of the important causes of heart failure in patients with acute MI, which eventually increases mortality and morbidity. [2]

MI can cause the migration of neutrophils, macrophages, and other cells into the infarct zone, leading to intracellular signaling and neurohormonal activation and subsequently resulting in the inducement of the inflammatory response. [3] Post-MI remodeling has been divided into an early phase (within 72 h) and a late phase (beyond 72 h). Inflammatory mechanisms play a critical role in the early phase. Late remodeling induces the LV spherically and is associated with time-dependent dilatation, the distortion of the ventricular shape, and hypertrophy. The failure to normalize wall stress creates progressive dilatation and a decline in the contractile function; consequently, more recent studies have focused on anti-inflammatory treatment for LV remodeling. [4]

According to previous studies, important parameters in primary LV remodeling and inflammation are the degradation of the intermyocyte collagen struts by serine proteases and the activation of matrix metalloproteinases (MMPs), which are released from neutrophils. Research has demonstrated that MMP levels in acute STEMI increase and that the inhibition of MMPs and the tissue inhibitors of metalloproteinases promotes LV remodeling in the wake of STEMI. [5,6]

The expression of MMP-2 and MMP-9 increases in pressure overload (LV hypertrophy), and the increased MMP expression and activation has been shown to initiate heart failure progression in various experimental models and in humans. The data regarding MMP inhibition are, however, somewhat controversial. Several studies have shown that MMP inhibition or gene inactivation reverses LV remodeling and dysfunction. [7,8]

Doxycycline is a broad MMP inhibitor and improves LV remodeling. A chemically modified and semisynthetic tetracycline, doxycycline is used for its antibacterial properties and its ability to inhibit the transformation of pro-MMPs to active MMPs. Various animal studies have shown that not only are anti-inflammatory agents crucial in stabilizing the vulnerable plaques of the aorta but also they can prevent the firm rupturing of cerebral aneurysms. [9] MMP-9 is known both for its predictive value in the cardiac complications of LV remodeling and for its use as a risk stratification marker. [10-12] Moreover, some studies have claimed that doxycycline can decrease oxidative stress. [13]

A variety of procedures are drawn upon to evaluate LV remodeling such as magnetic resonance imaging, perfusion scan, speckle-tracking echocardiography (STE), and stress echo with dobutamine. Given the safety and availability of echocardiography, today STE is deemed a new approach to the assessment of myocardial function. This imaging modality is based on an evaluation of torsion and deformation factors and may be able to detect exact degrees of functional impairment in ischemic tissues such as those discovered by myocardial perfusion imaging. Global and regional strains have been shown to associate well with visual wall motion abnormalities in patients with acute MI, non-coronary chest pains, or dilated cardiomyopathy. Many studies have recommended STE over other procedures for the measurement of LV remodeling; in addition, recent investigations have introduced torsion parameters as a sensitive approach for anticipating LV remodeling. [13-15]

It has been proven that LV twist is a highly sensitive and specific procedure for the measurement of LV remodeling in a variety of cases. [12,16]

Cerisano et al [16] showed improvement in the left ventricular end-diastolic volume (LVEDV)

parameters and the limitation of the infarcted area after 6 months due to a short (7 d) treatment with doxycycline. Some other studies have reported the positive effects of doxycycline in patients after coronary artery bypass graft surgery. [17,18] Given the importance of LV remodeling, in the present study, we utilized STE—as a harmless and sensitive procedure—to measure the effects of doxycycline on the LV torsion parameters in patients undergoing primary percutaneous coronary intervention (PCI).

METHODS

From 2015 to 2016, a total of 60 patients were randomly selected (based on the inclusion and exclusion criteria) from among all patients (450 patients in 1.5 years) with STEMI undergoing primary PCI at Rajaie Cardiovascular, Medical, and Research Center. All the subjects received complete information regarding the study protocol and volunteered to participate in the current study on the understanding that they could quit at any point during the study. The study population was divided into 2 different groups: experimental and control.

The inclusion criteria were comprised of anterior STEMI, primary PCI performed on the left anterior descending artery, and a left ventricular ejection fraction (LVEF) > 30%. The exclusion criteria consisted of old MI, cardiogenic shock, liver and renal diseases, doxycycline sensitivity, and poor echocardiographic views. This was a balanced block randomized clinical trial (by 4 blocks). Neither the doctors nor the patients were aware of the group classification in order for the study to be a double-blind clinical trial. The experimental group (n = 30) received doxycycline at a dose of 100 mg twice a day for 7 days, while the control group simultaneously received a placebo twice a day for 7 days.

Figure 1 display a summary of the methodology in this study.

Upon hospitalization, all the patients were evaluated by STE and transthoracic echocardiography (TTE) as soon as possible. Conventional M-mode echocardiographic measurements for the LV and the left atrium (LA) were obtained from the left parasternal long-axis view at the basal level. The LVEF was calculated visually. Two-dimensional imaging (appropriate depth, gain, and pulse repetition [frequency = .40 f/s) in the apical 4-, 3-, and 2-chamber views was used to assess torsion, basal rotation, apical rotation, and twist in the LV, and all these data were recorded precisely. After 40 days, STE was performed again for the patients, so that all the factors in 2D echocardiography and LV torsion were assessed for a second time. Finally, all the data were compared in order to determine the effects of doxycycline on LV remodeling during the trial. The echocardiographic data were analyzed on the first day and at the end of the 40-day period by an expert technician.

Statistical Analysis

The continuous variables were expressed as the mean ± the standard deviation (SD). The conventional echocardiographic parameters at baseline and 40 days after the administration of doxycycline were analyzed using the paired *t*-test. The strain parameters of each group at baseline and 40 days after the administration of doxycycline were also analyzed using the paired *t*-test, the χ^2 test, and the Mann–Whitney *U* test with SPSS, version 20. Likewise, multivariable analyses were implemented using logistic regression statistical samples.

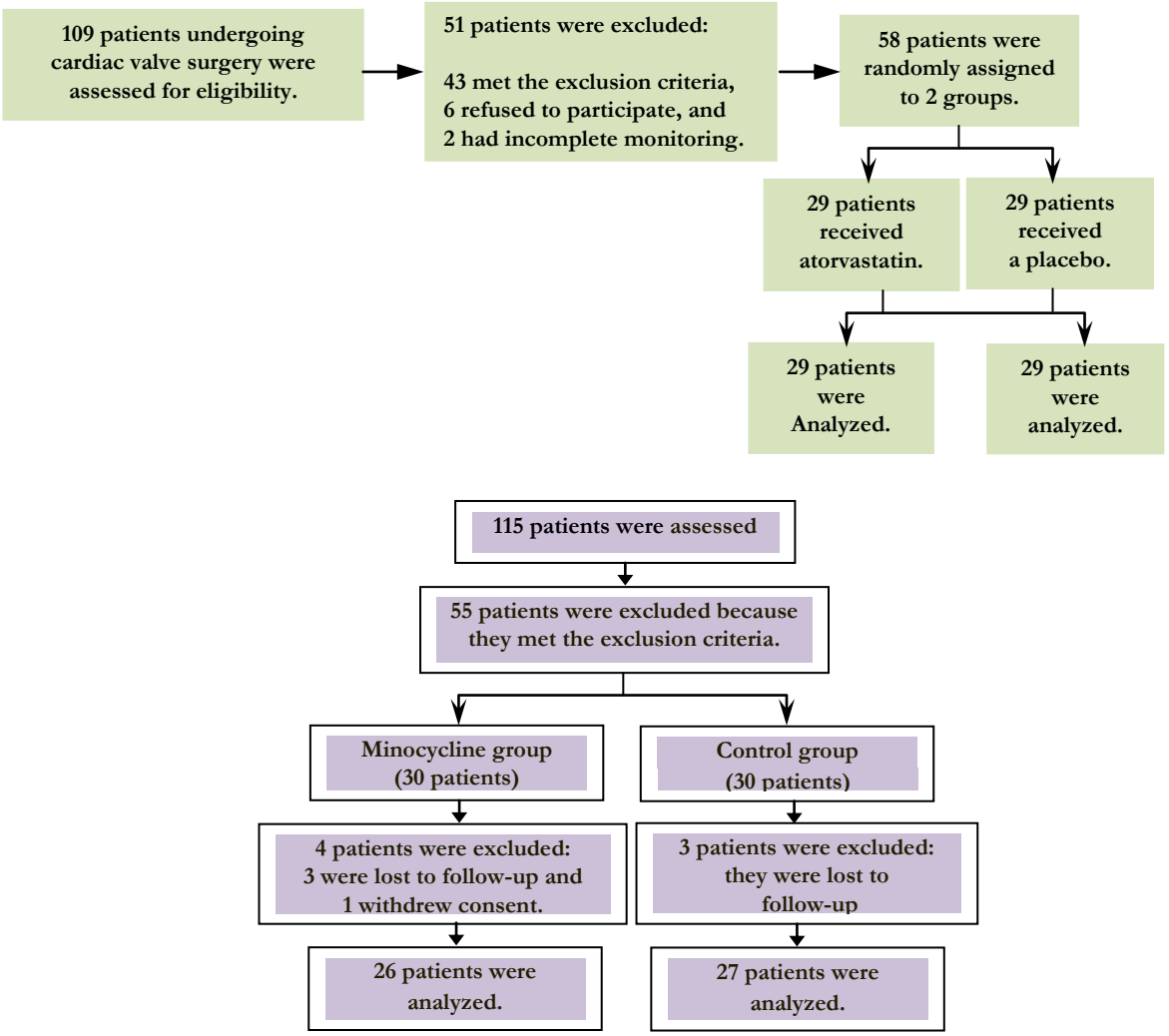

Figure 1. The patients were classified according to this flowchart.

RESULTS

Initially, 68 patients were recruited in the current study on the basis of the study inclusion and exclusion criteria; however, 8 of them quit the trial. Therefore, 60 patients (75% male) were analyzed. A history of hypertension was reported in 40% of the study population, diabetes in 38%, and dyslipidemia in 36%. The distribution of the patients' history and clinical features is depicted in Table 1. There were no statistically significant differences in the demographic characteristics between the experimental and control groups ($P = 0.05$).

Table 1. Characteristics of the control and experimental groups

	Control Group	Experimental Group	*P* value
Sex	63	86	0.03
Age	53.7	56.1	0.07
Hypertension	36%	43%	0.6
Diabetes	36%	40%	0.79
Dyslipidemia	40%	33%	0.59

Echocardiographic Findings

Table 2 demonstrates the mean 2D echocardiographic findings in terms of the LVEF, the LVEDV, the left ventricular end-systolic volume (LVESV), and the left atrial volume (LAV) initially on hospitalization and then 40 days afterward.

Table 2. Echocardiographic alterations in the control and experimental groups

	First Day			Day 40		
	Control Group	Experimental Group	*P* value	Control Group	Experimental Group	*P* value
LAV (mL)	42.1±3.5	41.4±5.7	0.57	53.2±6.4	50.2±4.3	0.03
LVESV (mL)	79.1±9.1	76.2±8.9	0.21	88.9±6.9	83.2±9.9	0.01
LVEDV (mL)	128±19.1	122±14.3	0.2	149±13.8	140±18.1	0.03
EF (%)	35-40	35-40	0.12	35-40	40-45	0.08
Apical	6.7±1.6	7±1.6	0.43	7.2±1.8	8.4±1.9	0.02
Basal	8.5±2	8.9±1.9	0.36	8.2±1.7	9.3±2.1	0.03
Twist	15.2±3.6	16±3.5	0.38	15.5±3.4	17.7±3.9	0.02
Torsion	1.97±0.4	2.1±0.4	0.27	1.93±0.3	2.27±0.4	0.002

LAV, Left atrial volume; LVESV, Left ventricular end-systolic volume; LVEDV, Left ventricular end-diastolic volume; EF, Ejection fraction

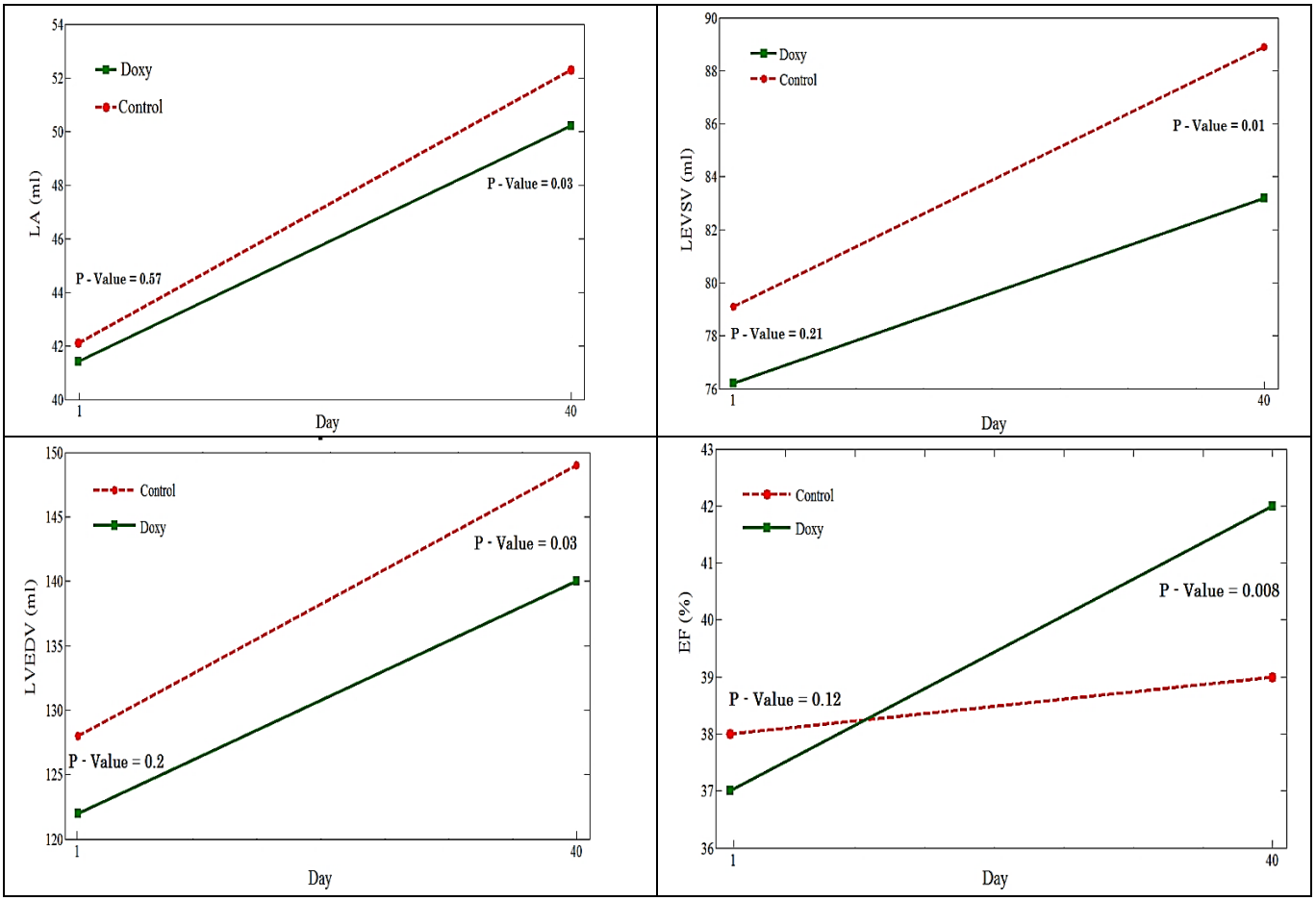

Figure 2. Echocardiographic parameters: A) LAV, B) LVESV, C) LVEDV, D) EF
LAV, Left atrial volume; LVESV, Left ventricular end-systolic volume; EF, Ejection fraction

The *t*-test results (Fig. A-2) revealed that the LAV was not statistically significantly different between the 2 study groups on the first day (42.1 mL in the control group vs 41.4 mL in the experimental group; $P = 0.57$). Conversely, 40 days later, the differences between the 2 groups in terms of the LAV increased (53.2 mL in the control group vs 50.2 mL in the experimental group; $P = 0.03$).

As is illustrated in Figure B-2, the 2 study groups were statistically significantly different from each other as regards the LVESV: the mean LVESV rose from 79.1 mL on day 1 to 89.9 mL on day 40 in the control group, while it increased from 76.2 mL on day 1 to 83.2 mL on day 40 (P = 0.21 on day 1 vs P = 0.01 on day 40).

As is demonstrated in Figure G-2, the mean LVEDV rose in both groups: from 128 mL on day 1 to 149 mL on day 40 in the control group and from 122 mL on day 1 to 140 mL on day 40 in the experimental group (P = 0.2 on day 1 vs P = 0.03 on day 40).

As is shown in Figure G-2, the mean LVEF was about 35%–40% on day 1 in both groups. However, on day 40, the mean LVEF was 35%–40% in the control group and 40%–45% in the experimental group (P = 0.008).

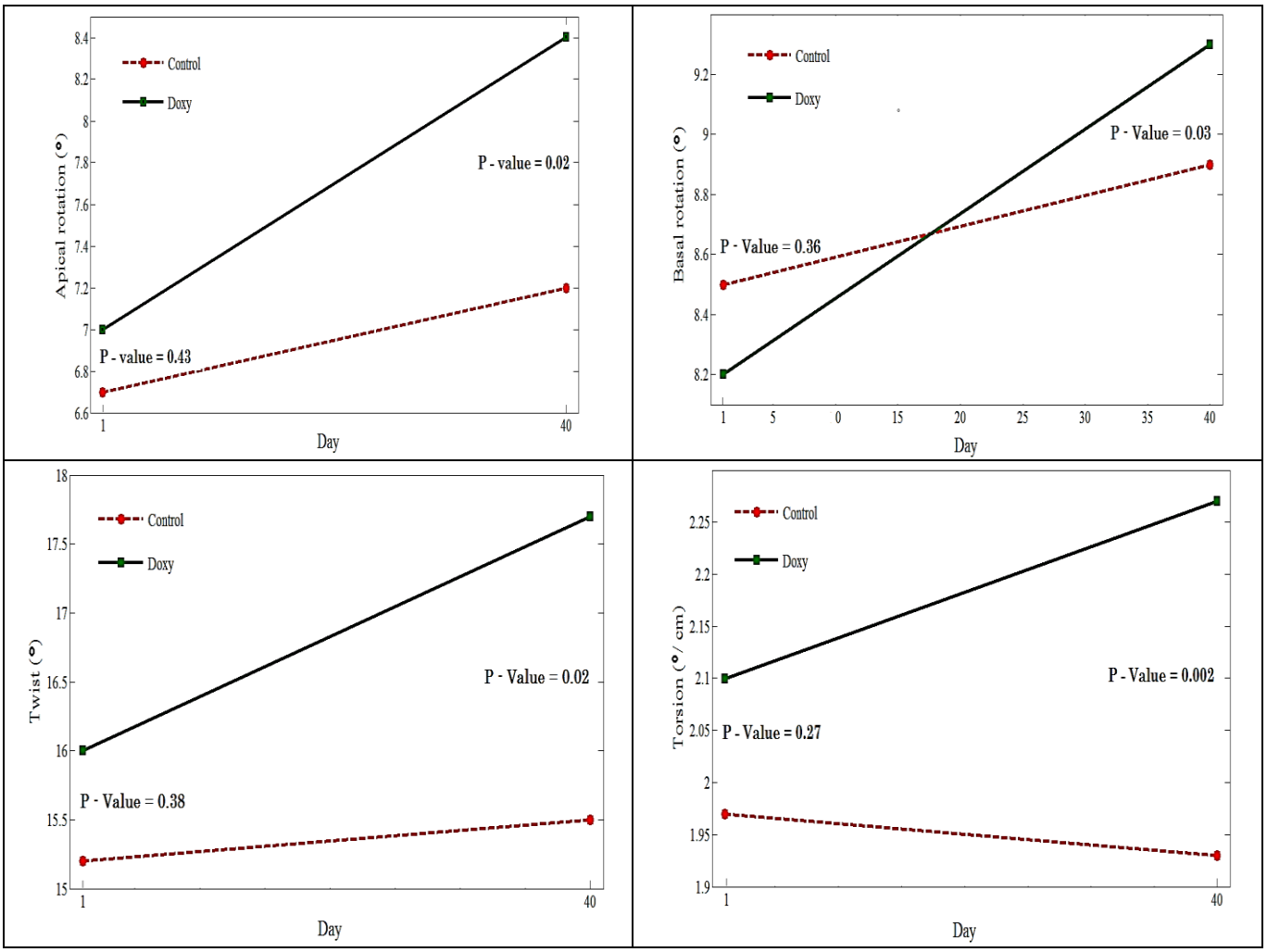

Figure 3. A) speckle-tracking echocardiography, B) apical rotation, C) basal rotation, D) twist, E) torsion

STE

Figure 2 depicts the mean LV apical and basal rotation, as well as the mean LV twist and torsion, measured by STE on day 1 and on day 40.

As is depicted in Figure 3-A, the mean LV apical rotation in the control group was 6.7° on day 1 and 7.2° on day 40, whereas the mean LV apical rotation changed from 7° on day 1 to 8.4°

on day 40 in the experimental group (P = 0.43 on day 1 vs P = 0.02 on day 40).

As is illustrated in Figure 3-B, the mean LV basal rotation was 8.5° in the control group and 8.9° in the experimental group on the first day (P = 0.36). Nonetheless, on day 40, this value increased to 9.3° in the experimental group, while it decreased in the control group (P = 0.02).

The mean LV twist, calculated by subtracting apical torsion from basal rotation, was 15.2 in the control group and 16 in the experimental group on the first day, and it changed to 15.5 in the control group and 17.7 in the experimental group on the 40th day (P = 0.38 on day 1 vs P = 0.02 on day 40).

The difference in the mean LV torsion between the 2 study groups was calculated to be approximately 0.13 (1.97 in the control group vs 2.1 in the experimental group; P = 027). On the 40th day, this difference reached 0.34 (1.93 in the control group vs 2.27 in the experimental group; P = 0.002) (Fig. 3-D).

DISCUSSION

In the present double-blind randomized control trial, we demonstrated the effects of the early administration of short-term doxycycline therapy in patients undergoing primary PCI on TTE parameters (LV torsion and twist). Our results showed that prescribing 100 mg of doxycycline twice a day for 7 days to this group of patients makes significant differences in TTE parameters of LV torsion and twist on the 40th postprocedural day. Indeed, the mean values of the LAV, the LVESV, and the LVEDV in our experimental group increased less than those in our control group. Further, the LVEF increased more significantly in the experimental group than in the control group. Additionally, an assessment of LV torsion parameters in both groups demonstrated significant differences in LV apical/basal rotation and LV twist and torsion between the 2 groups: LV apical/basal rotation and LV twist and torsion in the experimental group increased more significantly than those in the control group. The phenomenon of LV remodeling occurs after MI progressively. It causes an increment in the LV size (LVEDV and LVESV), although it diminishes the LV EF. Previous research has shown that a 20% increase in the LVEDV and a 10% increase in the LVESV are indices of LV remodeling. This phenomenon is prevented by treatments such as early revascularization, neurohormonal inhibition, and beta-blocker prescription. Nonetheless, according to recent studies, the effects of doxycycline on inflammatory parameters are not clear. [19]

Echocardiography is a broadly used clinical method for noninvasive imaging, especially in cardiovascular medicine, and STE is considered to be more useful than conventional echocardiography insofar as a quantitative evaluation of myocardial deformation by tracking myocardial movements is less angle-dependent. STE can identify subtle changes in contraction, which visual segmental functional assessments may not detect. The TIPTOP study is a recent review that underscored the advantages of doxycycline in LV remodeling. [20]

The TIPTOP study used a combination of modalities— including echocardiography and perfusion scans; however, we drew upon 2D echocardiography and STE as the most sensitive approach to the evaluation of LV remodeling and obtained compatible outcomes with the TIPTOP study.

Different procedures are used to evaluate LV remodeling such as magnetic resonance imaging, perfusion scans, STE, and the echo stress test with dobutamine. STE is one of the safest approaches because it is harmless and lacks radiation through the patient's body. Recent studies have selected LV torsion as a sensitive marker for the evaluation of LV systolic myocardial performance. [20,21]

Given the proven effects of doxycycline on inflammatory reactions in MI, early remodeling, and prohibitive effects on MMP,

this agent is recommended over other treatments. [4] Recent years have witnessed a growing interest in the effects of MMPs patients with MI, and MMP-8 is now regarded as a predictive factor for the diagnosis of cardiovascular diseases. Likewise, some investigations have proven that high levels of the tissue inhibitors of metalloproteinases can improve LV remodeling. [11, 22-25]

In light of the results from this and previous studies specifically working on patients with STEMI, we highly recommend that the beneficial outcomes of doxycycline be appraised in patients with acute coronary syndromes (eg, NSTEMI) or other cardiovascular conditions in the future.

In the current study, pantoprazole was prescribed to the patients to prevent gastrointestinal complications due to the consumption of doxycycline.

Study Limitations

Although the quality of 2D STE was acceptable, higher resolution for cardiac borders was still lacking. Automated speckle-tracking analysis is possible only with special software. Furthermore, since border tracing needs manual work, interobserver error is unavoidable.

Be that as it may, STE is a rapidly progressing imaging modality and 3D speckle-tracking may overcome many of the 2D strain shortcomings in the future.

REFERENCES

1. Braunwald's heart disease: a textbook of cardiovascular medicine DL Mann, DP Zipes, P Libby, RO Bonow- Elsevier Health Sciences: 2016:1063-1114.

2. Gajarsa JJ, Kloner RA. Left ventricular remodeling in the post infarction heart: a review of cellular, molecular mechanisms, and therapeutic modalities. *Heart Fail Rev.* 2011; 16:13–21.

3. Hayashi M, Tsutamoto T, Wada A, et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. Circulation. 2003; 107: 2559–2565.

4. Martin G. John Sutton, Norman Sharpe, Left Ventricular Remodeling After Myocardial Infarction Pathophysiology and Therapy, Circulation. 2000; 101: 2981-2988.

5. French BA, Kramer CM. Mechanisms of post infarct left ventricular remodeling. Drug Discov Today Dis Mech. 2007;4: 185–196.

6. Jhund PS, McMurray JJV. Heart failure after acute myocardial infarction: a lost battle in the war on heart failure? Circulation 2008:118, 2019–2021.

7. Torina AG, Reichert K, Lima F, de Souza Vilarinho KA, de Oliveira PP, do Carmo HR, de Carvalho DD, Saad MJ, Sposito AC, Petrucci O, Diacerein improves left ventricular remodeling and cardiac function by reducing the inflammatory response after myocardial infarction, PLoS One. 2015 Mar 27; 10(3): e 0121842.

8. Seropian IM, Toldo S, van Tassell BW, Abbate A. Anti-inflammatory strategies for ventricular remodeling following St-segment elevation acute myocardial infarction. J Am Coll Cardiol 2014;63:1593–1603.

9. Curci, J., D. Mao, D. Bohner, B. Allen, B. Rubin, J. Reilly, G. Sicard, and R. Thompson. Preoperative treatment with doxycycline reduces aortic wall expression and activation of matrix metalloproteinases in patients with abdominal aortic aneurysms. J. Vasc. Surg. 2000, 31:325-342.

10. Geerling G, Tauber J, Baudouin C, et al. The International Workshop on Meibomian Gland Dysfunction: report of the Subcommittee on Management and Treatment of Meibomian Gland Dysfunction. Invest Ophthalmol Vis Sci 2011; 52: 2050–64.

11. Halade, G. V., Jin, Y. F. & Lindsey, M. L. Matrix metalloproteinase (MMP)-9: a proximal

biomarker for cardiac remodeling and a distal biomarker for inflammation. Pharmacol. Ther. 2013, 139, 32–40.

12. Fan G.C., Zhou X., Wang X., Song G., Qian J., Nicolaou P., Chen G., Ren X., Kranias E.G. Heat shock protein 20 interacting with phosphorylated akt reduces doxorubicin-triggered oxidative stress and cardiotoxicity. Circ. Res. 2008; 103: 1270–1279.

13. Sitia S, Tomasoni L, Turiel M. Speckle tracking echocardiography: A new approach to myocardial function. World J Cardiol. 2010; 2:1–5.

14. Abduch MC, Alencar AM, Mathias W, Jr, Vieira ML. Cardiac mechanics evaluated by speckle tracking echocardiography. Arq Bras Cardiol. 2014; 4: 403–412.

15. Opdahl, T. Helle-Valle, H. Skulstad, and O. Smiseth, "Strain, strain rate, torsion, and twist: echocardiographic evaluation," Curr Cardiol Rep, 2015, vol. 17(3):15.

16. Cerisano G, Buonamici P, Valenti R, Sciagrà R, Raspanti S, Santini A, Carrabba N, Dovellini EV, Romito R, Pupi A, Colonna P, Antoniucci D. Early short-term doxycycline therapy in patients with acute myocardial infarction and left ventricular dysfunction to prevent the ominous progression to adverse remodelling: the TIPTOP trial. Eur Heart J. 2014 Jan; 35(3):184–191.

17. Kormi I, Alfakry H, Tervahartiala T, Pussinen PJ, Sinisalo J, Sorsa T. The effect of prolonged systemic doxycycline therapy on serum tissue degrading proteinases in coronary bypass patients: a randomized, double-masked, placebo-controlled clinical trial. Inflamm Res. 2014 May; 63(5):329-34.

18. Dong M, et al. Doxycycline stabilizes vulnerable plaque via inhibiting matrix metalloproteinases and attenuating inflammation in rabbits. PLoS One. 2012; 7(6).

19. Nucifora G., Ajmone Marsan N., Bertini M.; Reduced left ventricular torsion early after myocardial infarction is related to left ventricular remodeling. Circ Cardiovasc Imaging. 2010(3):433-442.

20. Jang JY, et al. Serial assessment of left ventricular remodeling by measurement of left ventricular torsion using speckle tracking echocardiography in patients with acute myocardial infarction. Cardiol. 2010 Oct 1;106(7):917-23.

21. Cerisano, G., Buonamici, P., Gori, et al, Matrix metalloproteinases and their tissue inhibitor after reperfused ST-elevation myocardial infarction treated with doxycycline. Insights from the TIPTOP trial (2015) International Journal of Cardiology, 197, 147-153.

22. Yaghoubi, A., Safaie, N., Azarfarin, R., Alizadehasl, Azin., Golzari, S.E. valuation of cardiovascular diseases and their risk factors in hospitalized patients in East Azerbaijan province, Northwest Iran: A review of 18323 cases . Journal of Tehran University Heart Center, 2013, 8(2):101-105

23. Mirinejad, M., Azarfarin, R., Azin Alizadehasl. . Cisatracurium in cardiac surgery - Continuous infusion vs. bolus administration; Middle East Journal of Anesthesiology; 2007, 19(3):563-572.

24. Azarfarin, R., Sheikhzadeh, D., Mirinazhad, M., Bilehjani, E., Alizadehasl, Azin. Do nondiabetic patients undergoing coronary artery bypass grafting surgery require intraoperative management of hyperglycemia? Acta Anaesthesiol Taiwan. 2011 Jun;49(2):41-5. doi: 10.1016/j.aat.2011.05.009. Epub 2011 Jun 24.

25. Joyce E, Leong DP, Hoogslag GE, van Herck PL, Debonnaire P, Abate E, et al. Left ventricular twist during dobutamine stress echocardiography after acute myocardial infarction: association with reverse remodeling. Int J Cardiovasc Imaging. 2014; 30: 313–322.