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## **Research** Article



# Intra-Arterial Labetalol and Nitroglycerin in Preventing Radial Artery Spasm Following Transradial Angiography: A New Approach

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## Abstract

*Background:* Radial artery spasm (RAS) resulted from decreasing blood flow and activation of vasomotor system leads to a decrease in artery diameter, perfusion and patency, and increase the risk of procedure failure. In this study, we investigated the effects of intra-arterial administration of nitroglycerin and labetalol on radial artery diameter, RAS, and pain intensity in patients undergoing diagnostic radial angiography.

*Methods:* Sixty-four patients randomly enrolled into one of the nitroglycerin (150  $\mu$ g) or labetalol (500  $\mu$ g) groups. The radial artery size, and the incidence of RAS were measured before, immediately after puncture, and at the end of treatment. Pain intensity was evaluated using a visual-analog-scale (VAS) at the end of the procedure. Hemodynamic status before, and during the procedure was also recorded.

**Results:** Labetalol causes a significantly larger increase in radial diameter than nitroglycerin immediately after intra-arterial injection  $(2.24\pm0.58 \text{ mm vs}. 1.65\pm0.39 \text{ mm}, \text{P-value}<0.001)$ . The rate of RAS immediately after vasodilator administration in the labetalol group was 3.1% vs. 12.5% in the nitroglycerin group (P-value=0.355), but the overall incidence (immediately after administration+ at the end of procedure) did not show a statistically significant difference (53.125% vs 31.25% respectively, P-value=0.076). The VAS score did not show a significant difference between two groups (1.15\pm0.44 in nitroglycerin vs. 1.50\pm0.91, P-value=0.063).

*Conclusion:* Labetalol increases radial artery diameter more than nitroglycerin. However, the efficacy of labetalol in terms of RAS incidence, and patients' pain was similar to nitroglycerin. Therefore, intra-arterial labetalol could be considered as one of the therapeutic options in clinical practice in order to reduce RAS and procedure failure.

## Introduction

Today, transradial access procedure is one of the most widely used methods in cardiovascular interventions.<sup>1,2</sup> The advantages of transradial access include lower bleeding risk, easy access to coronary targets, reduced hospitalization period, decreased mortality rate, and major adverse cardiac events (MACE), and higher patency compared to other coronary access.<sup>1-7</sup> Additionally, one study showed that the rate of contrast media induced-nephropathy and acute kidney injury in transradial access was less than femoral access.<sup>8</sup>

Radial artery spasm (RAS) is one of the most important complications of radial artery access, which can lead to the failure of procedure. The incidence rate of RAS has been reported between 4-14.7%, which can occur in acutely or delayed manner.<sup>2,5,9</sup> Reduced blood flow in radial artery canal leads to shear stress and procedure failure, and subsequent activation of vasomotor systems causes spasm

and narrowing of the vessel diameter, even in some cases diffuse narrowing of the artery (string sign). Vasospasm leads to patients' discomfort, pain, vascular hypoperfusion, intima hyperplasia, and harmful effects on long-term patency.<sup>9-11</sup>

Nitroglycerin is one of the medications that its beneficial effect on RAS, radial diameter increase, and pain relief has been proven in many studies.<sup>1,9,12,13</sup> Nitroglycerin is a vasodilator which releases NO, stimulates the activity of guanylate cyclase and cGMP leading to relaxation of smooth muscles of the vessels.<sup>14</sup> Nitroglycerin relieves the spasm induced from various pathways such as thromboxane A2, endothelin and  $\alpha$ -adrenoreceptors.<sup>15</sup>

Labetalol is a selective beta-1 blocker, and post-synaptic inhibitor of alpha-1 receptors with intrinsic membrane stabilization and sympathomimetic properties. It has been shown that labetalol has an obvious effect on the reduction of spasm caused by vasoconstrictor substances

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in in-vitro environment, but there is no in-vivo study in this regard. The results of the above study showed that the relaxation response to labetalol was significantly higher than propranolol and nebivolol. Korkmaz et al. stated that labetalol relaxant effect on radial artery rings is through its effect on potassium channels activated by calcium.<sup>4</sup>

The present study is the first in-vivo study, which investigates the effects of intra-arterial labetalol on the incidence of RAS, radial artery diameter changes, and pain in patients undergoing diagnostic radial angiography and comparing it with intra-arterial nitroglycerin with a long history of use in RAS prophylaxis.

## **Materials and Methods**

## Study design, population and outcomes

This study was a randomized double-blind clinical trial conducted in Mazandaran Heart Centre (Sari, Iran) from November 2018 to February 2019.

During this period, 64 patients aged 18 and above with normal Barbeau test who were admitted for elective diagnostic transradial angiography and randomly enrolled into two groups based on block-randomization [nitroglycerin (N=32, 150µg) or labetalol (N=32, 500µg)]. Patients with any history of radial artery access use in previous procedures, peripheral vascular disease, history of Raynaud's, ejection fraction (EF%)<40%, heart rate at rest<55 beat/min, systolic blood pressure<90 mmHg, history of liver disease, any history of allergic reactions to nitroglycerin or labetalol, and who not satisfied to participate in the study, were excluded.

The primary endpoint was the rate of incidence and severity of RAS between two groups. The secondary endpoints were the effect of labetalol and nitroglycerin on radial artery diameter changes as well as patients' pain intensity based on visual-analog-scale (VAS).

Ezhumalai et al. study was used to determine the sample size based on diameter changes.16 Based on the 99% confidence level and 90% test power for the two test domains using the mean comparison formula in "G-power software", the sample size was estimated [64 cases (32 patients in each group)]. Patients were divided into two groups by block-randomization method. Eight blocks consisting of 8 patients were created by "random allocation software" using sequential codes. Then, eligible patients were randomly enrolled in each block. One of Cathlab (angiography room) staff prepared the medications and provided them to the specialist based on blockrandomization. Angiographic specialist blindly prescribed the medications to the patients, and the investigator recorded the data without knowing the type of prescribed medication. The statistical analyst also was unaware of the interventionist groups.

## **Procedure protocol**

All patients' data including demographic information, history of medications, diseases, laboratory findings, and EF% were recorded. In order to assess hemodynamic stability before angiography, patients' blood pressure, and heart rate were monitored.

All patients received moderate sedation with 1mg midazolam (IV), and local anesthesia with 1cc xylocaine 2% (SC) before arteriotomy. All cases received 50–70 U/ kg intravenous unfractionated heparin. Arterial access was achieved by using 21G (6F),  $0.018^{"}/0.46$  mm (Prelude/ NERTMEDICAL<sup>TM</sup>) needle and sheath, and  $0.035^{"}/0.89$  mm guidewire. Patients randomly entered into one of intraarterial nitroglycerin (150 µg) or labetalol (500 µg) groups. The medications injected immediately after the arterial puncture. The angiography procedure was performed only by one attending interventional cardiologist to remove the technical variations between operators. Hemodynamic status was monitored during angiography and any changes in blood pressure or heart rate were recorded.

In this study, we measured the change of systolic and diastolic blood pressure, and heart rate expressed as a subtraction of the secondary value of the initial value. The number of punctures, puncture time (second), fluoroscopy time (minute), radiation dose ( $\mu$ Gy), and dose area product (DAP) ( $\mu$ Gym2) were recorded after catheterization. Any tortuosity, coronary anomalies, and success in the procedure were recorded at the end of work.

## Angiographic evaluation of radial artery diameter

Measuring the size of radial artery (mm) after calibration of the sheath diameter as an absolute value (mm) was performed in three steps in the narrowest site of artery: 1) before vasodilator administration, 2) immediately after vasodilator administration, and 3) at the end of the procedure by a blind observer through angiographic method (Figure 1).

## **Evaluation of RAS**

The incidence and severity of RAS in each group was evaluated in three stages: 1) before vasodilator administration, 2) immediately after vasodilator administration, and 3) at the end of angiography, and regarding severity in four classifications: 1) no spasm, 2) mild spasm (stenosis in radial diameter <30%), 3) moderate spasm (stenosis in radial diameter between 30-70%), and 4) severe spasm (stenosis in radial diameter >70%) (Figure 1).

## **Evaluation of pain**

Patients' pain intensity was measured at the end of angiography via VAS scale. VAS is a one-dimensional marker for assessing the severity of pain determined by the patient. This scale is a 10 cm line between painless to maximum pain range, and the interpretation of pain intensity is based on the marked point. The higher VAS score indicates higher pain severity (Figure 1).

## Statistical analysis

Quantitative variables are represented as Mean±SD and qualitative variables as percentage. The normality of data

#### Labetalol and Nitroglycerin in Radial Artery Spasm

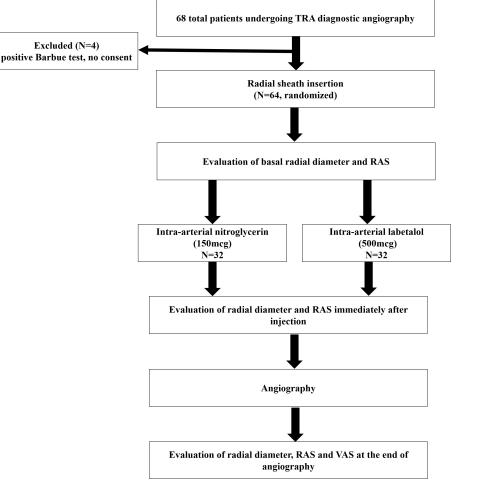


Figure 1. Study design for pre-dilation and radial quantitative angiography assessment. [trans-radial angiography (TRA), visual-analogscale (VAS), and radial artery spasm (RAS).

distribution was carried out by the Kolmogorov-Smirnov test. The comparison of quantitative variables between two groups was investigated using independent t-test or its non-parametric equivalent, Mann-Whitney test, and in qualitative variables was done by Chi-square/Fisher exact test. Comparison of the diameter changes during the procedure in each group was performed by repeated measurement test or its equivalent Friedman test, repetitive measurement test. As well as, the comparison of changes between two groups regarding variables of diameter and intensity of RAS was performed by generalized estimating equation (GEE) test. Ranked logistic regression was used to adjust the effect of RAS before medications administration on subsequent spasm incidence. All statistical analyses were conducted by using the software SPSS version 23 (SPSS Inc., Chicago, IL, USA) and P-value <0.05 were considered significant.

## Results

## **Evaluation of RAS**

All patients' demographic information, history of medications, diseases, laboratory findings, and EF% are presented in (Table 1). The rate of RAS incidence before administration of vasodilator in the nitroglycerin

group was 9.375% and in labetalol group 53.75%, which showed a significant difference (P-value=0.002). However, immediately after the administration of vasodilator, the incidence of RAS in nitroglycerin group was 12.5%, and in labetalol group was only 3.1%, but this difference was not statistically significant (P-value=0.355) (Figure 2). The age (P-value=0.024), and systolic blood pressure before initiation of angiography (P-value=0.004) showed a significant effect on the incidence of spasm after intraarterial medication. There was no significant difference between two groups in terms of the history of nitroglycerin use which could be considered as a confounding factor (P-value=0.590). Analysis of the correlation between the history of nitroglycerin use, and RAS did not show any statistically significant result [(P-value before vasodilator injection =0.570), (P-value immediately after vasodilator injection =0.158), and (P-value at the end of procedure =0.634)]. As well as, the fluoroscopy duration (P-value=0.018) showed a significant correlation with the overall incidence of RAS (total incidence of RAS before and after vasodilator administration). The diameter of the radial artery at the end of the procedure showed a significant correlation with the incidence of spasm after medication administration.

The nitroglycerin group experienced a significantly

	Nitroglycerin Labetalol		
	group (95% CI)	group (95% CI)	P- value
Age (years)	59.06±10.99	57.59±12.31	0.617
	(55.10-63.03)	(53.15-62.03)	
BMI <sup>a</sup> (kg/m <sup>2</sup> )	27.73±4.50	27.38±3.29	0.728
Divil <sup>-</sup> (Kg/III <sup>-</sup> )	(26.10-29.35)	(26.20-28.57)	
EF <sup>▶</sup> (%)	53.00±6.65	54.25±7.24	0.312
	(50.60-55.39)	(51.63-56.86)	
Smoking	1(3.1)	5(15.6)	0.196
Oppium addict	0(0)	2(6.3)	0.492
Disease history:			
Diabetes mellitus	10(31.3)	10(31.3)	1.000
Hypertension	17(53.1)	14(43.8)	0.453
Cardiovascular disease	8(25)	7(21.9)	0.768
Dyslipidemia	17(53.1)	15(46.9)	0.617
Medication history:			
Aspirin	30(93.8)	25(78.1)	0.148
Clopidogrel	10(31.3)	10(31.3)	1.000
Statin(s)	24(75)	20(62.5)	0.281
ACEI(s)°/ARB(s)d	16(50)	12 (37.5)	0.313
Nitroglycerin	11(34.4)	9(28.1)	0.590
Beta-blocker(s)	23(71.9)	19(59.4)	0.292
Others	18(56.3)	21(65.6)	0.442
Laboratory findings	6:		
	20.03±15.1	18.28±14.02	0.696
ESR <sup>e</sup> (mm/h)	(14.58-25.47)	(13.22-23.33)	
Triglycerides	144.34±70.16	141.09±112.84	0.151
(mg/dl)	(119.04-169.64)	(100.40-181.77)	
Chalasteral (mc/dl)	160.62±33.86	160.03±40.17	0.949
Cholesterol (mg/dl)	(148.41-172.83)	(145.54-174.51)	

Table 1. Baseline characteristics of patients [Mean±SD or N(%)].

 $^{\rm s}\text{body}$  mass index /  $^{\rm b}$  ejection fraction /  $^{\rm c}$  angiotensin converting enzyme inhibitor(s)/  $^{\rm d}$  angiotensin receptor blocker(s) /  $^{\rm e}$  erythrocyte sedimentation rate.

lower severity RAS than labetalol group before the injection (P-value=0.009), and at the end of the procedure (P-value=0.021) (Figure 2). After adjusting for the effect of primary spasm, the incidence of RAS immediately after intra-arterial administration did not show a significant difference (P-value=0.054), whereas at the end of angiography, the difference was significant in the labetalol group compared to nitroglycerin (P-value=0.005). In addition, the incidence of disseminated spasm in labetalol was significantly higher than nitroglycerin at the end of angiography (43.75% vs. 21.9%).

## Evaluation of radial artery diameter changes

The basal diameter of radial artery prior to injection did not show a significant difference between two groups (P-value=0.087). However, this difference was dramatic immediately after intra-arterial injection (P-value<0.0001), and the secondary size of the radial artery in the patients receiving labetalol was higher than nitroglycerin ( $2.24\pm0.58$ mm vs.  $1.65\pm0.39$  mm). However, at the end of angiography, the results were similar (P-value=0.40) (Table 2).

#### **Evaluation of pain intensity**

In terms of pain intensity (VAS scale) at the end of the procedure, the mean score in nitroglycerin group was lower than labetalol ( $1.15\pm0.44$  vs.  $1.50\pm0.91$ ). However, no statistically significant differences were seen (P-value= 0.063) (Table 2).

## Patients' hemodynamic status

All patients in both groups were stable hemodynamically, and no significant differences were observed in both groups before angiography (Table 2). Mean heart rate after vasodilator administration reduced by  $-1.53\pm2.21$  beat/min in nitroglycerin group and  $-1.78\pm2.97$  beat/min in labetalol group after vasodilator injection, and no significant difference has been seen between two groups (P-value=0.689). As well as, systolic and diastolic blood pressure in the labetalol group has dropped significantly compared to nitroglycerin (P-value=0.000) (Table 2).

## Discussion

This trial was the first in-vivo study investigating the effect of labetalol on RAS, radial diameter changes, patients' pain, and the hemodynamic status during angiography, and its differences with nitroglycerin in terms of mentioned parameters. Radial artery access is considered as a safe method for catheterization interventions in patients with adequate bilateral blood flow to the hand.<sup>14</sup> Lower risk of vascular complications, patients rapid ambulation, ability to use this method in obese individuals, people treated with a therapeutic dose of anticoagulants, and patients with spinal cord abnormalities spread the use of this method in cardiologic procedures.<sup>17</sup> But, RAS is the most important complication of this approach that affects the success of the procedure, and reduces the interventionists' willing to this method.<sup>18,19</sup>

The radial artery is classified as a type III artery mostly comprised of tunica media layer which is more prone to spasm and reduction in diameter in the exposure of vasoconstrictors than other artery types.<sup>19</sup> Various techniques such as reducing the diameter of the catheter or the use of hydrophilic coating sheaths have been used to reduce RAS. Still, these techniques have not been able to eliminate this complication. Therefore, many experts agree to pre or post-procedure administration of prophylactic vasodilators.<sup>4,14,19,20</sup>

The incidence of RAS immediately after medication in the present study was 12.5% in nitroglycerin and 3.1% in the labetalol group. A review study conducted in 2015 examined different intra-arterially regimens efficacy in reducing RAS showed that the incidence of RAS in the placebo group was similar to intra-arterial verapamil 2.5 mg (12%), but greater than verapamil 5 mg (4%). Whilst, regarding nicorandil, the incidence was higher than placebo (16% vs. 12%). But unlike the present study, the incidence of RAS in the nitroglycerin group was significantly lower (4% in 100 µg dose and 2% in 200 µg dose).<sup>5</sup>

The current study indicates a greater rate of RAS incidence

#### Labetalol and Nitroglycerin in Radial Artery Spasm

Table 2. Procedure characteristics and patients' hemodynamic data [Mean±SD or N(%)].

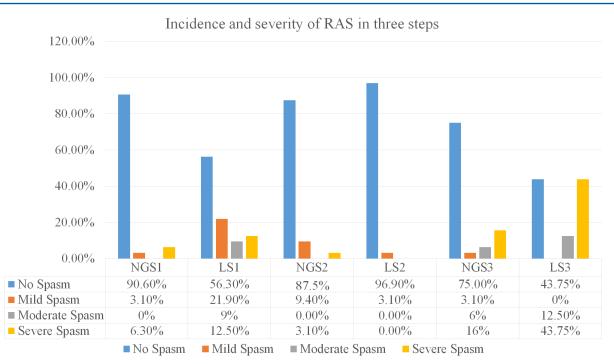
Nitroglycerin group (95%CI)	Labetalol group(95%CI)	P-value
147.25±22.39	$\begin{array}{c} 81.97\pm12. \\ (77.39-86.55) \\ 137.56\pm17.51 \\ (131.25-143.88) \\\hline 74.50\pm12.13 \\ (70.12-78.87) \\\hline \\ \hline \\ -1.78\pm2.97 \\ (-2.85\0.71) \\\hline \\ -12.15\pm22.10 \\ (-20.12\4.18) \\\hline \\ -4.78\pm6.95 \\ (-7.28\2.27) \\\hline \\ 11.64\pm13.25 \\ (6.86-16.42) \\\hline \\ 1.12\pm0.33 \\ (0.94-1.48) \\\hline \\ 4.32\pm4.00 \\ (2.88-5.77) \\\hline \\ 519.03\pm278.63 \\ (418.57-619.48) \\\hline \\ 3902.71\pm2388.48 \\ (3041.57-4763.85) \\\hline \\ 28(87.5) \\\hline \\ 21(53.125) \\\hline \\ 1.79\pm0.44 \\ (1.63-1.95) \\\hline \\ 2.24\pm0.58 \\ (2.03-2.45) \\\hline \\ 1.69\pm0.65 \\ (1.46-1.93) \\\hline \\ 1.50\pm0.91 \\\hline \end{array}$	0.28
(139.18-155.32)		
86.13±11.41	$\begin{array}{c} 81.97\pm12. \\ (77.39-86.55) \\ 137.56\pm17.51 \\ (131.25-143.88) \\ 74.50\pm12.13 \\ (70.12-78.87) \\ \hline \\ \\ -1.78\pm2.97 \\ (-2.85\0.71) \\ -12.15\pm22.10 \\ (-20.12\4.18) \\ -4.78\pm6.95 \\ (-7.28\2.27) \\ \hline \\ 11.64\pm13.25 \\ (6.86-16.42) \\ 1.12\pm0.33 \\ (0.94-1.48) \\ 4.32\pm4.00 \\ (2.88-5.77) \\ \hline \\ 519.03\pm278.63 \\ (418.57-619.48) \\ 3902.71\pm2388.48 \\ (3041.57-4763.85) \\ \hline \\ 28(87.5) \\ 2(6.3) \\ 1(3.1) \\ 1(3.1) \\ 3(9.4) \\ 31(96.9) \\ 17(53.125) \\ \hline \\ 1.79\pm0.44 \\ (1.63-1.95) \\ 2.24\pm0.58 \\ (2.03-2.45) \\ 1.69\pm0.65 \\ (1.46-1.93) \\ \end{array}$	0.058
(82.01-90.24)		
79.62±13.99	$\begin{array}{c} 81.97\pm12. \\ (77.39-86.55) \\ 137.56\pm17.51 \\ (131.25-143.88) \\\hline 74.50\pm12.13 \\ (70.12-78.87) \\\hline \\ \hline \\ -1.78\pm2.97 \\ (-2.85\0.71) \\\hline \\ -12.15\pm22.10 \\ (-20.12\4.18) \\\hline \\ -4.78\pm6.95 \\ (-7.28\2.27) \\\hline \\ 11.64\pm13.25 \\ (6.86-16.42) \\\hline \\ 1.12\pm0.33 \\ (0.94-1.48) \\\hline \\ 4.32\pm4.00 \\ (2.88-5.77) \\\hline \\ 519.03\pm278.63 \\ (418.57-619.48) \\\hline \\ 3902.71\pm2388.48 \\ (3041.57-4763.85) \\\hline \\ 28(87.5) \\\hline \\ 22(6.3) \\\hline \\ 1(3.1) \\\hline \\ 1(3.1) \\\hline \\ 3(9.4) \\\hline \\ 31(96.9) \\\hline \\ 17(53.125) \\\hline \\ \hline \\ 1.79\pm0.44 \\ (1.63-1.95) \\\hline \\ 2.24\pm0.58 \\ (2.03-2.45) \\\hline \\ 1.69\pm0.65 \\ (1.46-1.93) \\\hline \\ 1.50\pm0.91 \\\hline \end{array}$	0.073
(74.57-84.67)	(70.12-78.87)	
-1.53±2.21	-1.78±2.97	0.689
(-2.320.73)	(-2.850.71)	
0.03±0.40	-12.15±22.10	0.000
(-0.11_0.17)	(-20.124.18)	
-0.03±0.17	-4.78±6.95	0.000
(-0.09 0.03)	(-7.28 -2.27)	
· _ /		
17.92±21.36	$\begin{array}{c} (77.39-86.55) \\ 137.56\pm17.51 \\ (131.25-143.88) \\ 74.50\pm12.13 \\ (70.12-78.87) \\ \hline \\ \hline \\ -1.78\pm2.97 \\ (-2.85\0.71) \\ -12.15\pm22.10 \\ (-20.12\4.18) \\ -4.78\pm6.95 \\ (-7.28\2.27) \\ \hline \\ 11.64\pm13.25 \\ (6.86-16.42) \\ 1.12\pm0.33 \\ (0.94-1.48) \\ 4.32\pm4.00 \\ (2.88-5.77) \\ \hline \\ 519.03\pm278.63 \\ (418.57-619.48) \\ 3902.71\pm2388.48 \\ (3041.57-4763.85) \\ \hline \\ 28(87.5) \\ 2(6.3) \\ 1(3.1) \\ 1(3.1) \\ 3(9.4) \\ 31(96.9) \\ 17(53.125) \\ \hline \\ 1.79\pm0.44 \\ (1.63-1.95) \\ 2.24\pm0.58 \\ \hline \end{array}$	0.727
(10.22-25.63)		
1.06±0.24	1.12±0.33	0.395
	· · · ·	0.217
(2.34-3.66)	(2.88-5.77)	0.169
· · · · ·		
3.00±1.83 4.32±4.00   (2.34-3.66) (2.88-5.77)   446.34±284.52 519.03±278.63   (343.76-548.92) (418.57-619.48)   3638.62±1859.13 3902.71±2388.48		
1 /		0.692
( ,		
24(75)	28(87.5)	0.082
( )		
( /		0.238
	,	1.000
10(31.25)		0.076
1.61±0.38	1.79±0.44	0.087
,	47-1.75) (1.63-1.95)	
1.65±0.39	2.24±0.58	0.000
1.65±0.39 (1.51-1.79)		0.000
(1.51-1.79)	(2.03-2.45)	
(1.51-1.79) 1.58±0.41	(2.03-2.45) 1.69±0.65	
(1.51-1.79)	(2.03-2.45) 1.69±0.65 (1.46-1.93)	
	$\begin{array}{c} 147.25\pm22.39\\ \hline (139.18-155.32)\\ \hline 86.13\pm11.41\\ \hline (82.01-90.24)\\ \hline 79.62\pm13.99\\ \hline (74.57-84.67)\\ \hline \\ \hline \\ \hline \\ -1.53\pm2.21\\ \hline \\ (-2.32\0.73)\\ \hline \\ 0.03\pm0.40\\ \hline \\ (-0.11\_0.17)\\ \hline \\ -0.03\pm0.17\\ \hline \\ (-0.09\_0.03)\\ \hline \\ \hline \\ \hline \\ 17.92\pm21.36\\ \hline \\ (10.22-25.63)\\ \hline \\ 1.06\pm0.24\\ \hline \\ (0.97-1.15)\\ \hline \\ 3.00\pm1.83\\ \hline \\ (2.34-3.66)\\ \hline \\ 446.34\pm284.52\\ \hline \\ (343.76-548.92)\\ \hline \\ 3638.62\pm1859.13\\ \hline \\ (2968.33-4308.91)\\ \hline \\ \hline \\ 24(75)\\ \hline \\ 8(25)\\ \hline \\ 0(0)\\ \hline \\ 0(0)\\ \hline \\ 0(0)\\ \hline \\ 0(0)\\ \hline \\ 10(31.25)\\ \hline \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

<sup>a</sup>Dose area product/ b radial artery spasm/ c visual analogue scale.

after medication (including RAS immediately after vasodilator administration, and at the end of angiography) in the labetalol group compared to nitroglycerin. However, the difference was not statistically significant (P-value=0.076) (Table 2). Chen et al. study showed the incidence of spasm was 3.8% in (3000U heparin+100µg nitroglycerin) and 4.4% in (3000 U heparin+100µg nitroglycerin) which was not statistically significant (P-value=0.084), but both groups significantly differed from (3000 U heparin) (P-value<0.05).<sup>14</sup> Hizoh et al. did not find any differences between the administration of verapamil (5 mg) and placebo in terms of the incidence of RAS (1% vs. 1.7%, p-value=0.50).<sup>19</sup> The rate of RAS

before medication was higher in labetalol, that may indicate other predisposing factors for RAS in this group. However, after adjusting for the effect of spasm prior to the administration, RAS rate was still higher in the labetalol group.

In our trial, age (P-value=0.024), and patients' systolic blood pressure prior to the procedure (P-value=0.004) are considered as predisposing factors for the incidence of RAS. High systolic blood pressure cause elastin degradation, endothelial damage, increase the possibility of atherosclerosis, and significant changes in radial, and aortic pressure. This effect aggravates with aging and hypertension. Therefore, the total effects of these factors



**Figure 2.** Comparison of the severity of RAS between two groups. (P-value before vasodilator injection = 0.009), (P-value immediately after vasodilator injection = 0.355) and (P-value at the end of procedure = 0.021). [After adjusting for initial spasm effect: (P-value immediately after vasodilator injection = 0.054) (P-value at the end of procedure = 0.005)] (NGS1, NGS2, NGS3, LS1, LS2, and LS3): spasm before vasodilator injection, immediately after vasodilator injection and at the end of the procedure in nitroglycerin and labetalol groups, respectively).

affect the artery perfusion, and development of artery spasm.<sup>21</sup> Chen et al. introduced age, height, weight, history of smoking, and diabetes as risk factors of RAS.<sup>14</sup> Boyer et al. study showed a short height and low weight effect on the size of the radial artery, and the incidence of spasm.<sup>22</sup> Dharma et al. considered hormonal factors as influential factors in responding to vasodilators in patients undergoing transradial catheterization. Estrogen is one of the important factors affecting the endothelial function, causing vasodilatation through NO release and increasing its plasma concentration. In above study, authors stated that the use of nitroglycerin (as a NO donor) does not increase its concentration and will not affect the patency of the vessel. Exogenous NO, especially in young women with high estrogen levels, will not affect the vascular endothelium. But for older women with lower estrogen levels may be beneficial.<sup>23</sup> Our study confirms these results. There was no statistically significant correlation between the history of nitroglycerin use and incidence of spasm in all three steps in our study.

Radial artery manipulation, especially in patients with smaller artery size, damages the intima and media, and leads to vessel stenosis and RAS.<sup>13</sup> The study by Kiemeneij et al. showed that the administration of verapamil (5 mg)+nitroglycerin (200  $\mu$ g) did not differ significantly from no-vasodilator group in terms of radial artery diameter (P-value=0.79).<sup>24</sup>

In the present study, the mean size of the radial artery dramatically increased in the labetalol group compared to nitroglycerin immediately after intra-arterial injection  $(2.24\pm0.58$ mm vs.  $1.65\pm0.39$ mm, P-value<0.001) (Table 2).

The results of our study are similar to the results of Boyer et al. in which the size of the radial artery in the proximal, and narrowest portion of the artery was significantly greater in vasodilator group compared to no-vasodilator group.<sup>22</sup> Increasing the size of radial artery facilitates the catheter movements by reducing its friction with the vessel endothelium, thereby decreases the possibility of RAS occurrence, and failure of the procedure.<sup>13</sup> In the present study, despite increasing the size of the radial artery in the labetalol group, the severity of spasm immediately after injection did not differ significantly (P-value=0.355), and at the end of the procedure, the rate of severe, and diffuse spasm in labetalol group was higher (Figure 2).

Another instrument for evaluation of RAS is measurement of the severity of pain during sheath insertion, manipulation, and sheath removal which has been addressed in various studies.14,17,24 Although this is a qualitative criterion based on the assessment of the severity of pain by the patients, and may be influenced by variations in interpersonal judgments.17 As well as, factors such as gender, hormones differences, and stress conditions before and during the procedure, and the subsequent release of catecholamines also affecting the patients' pain and incidence of RAS.<sup>14</sup> In the current study, the VAS score was lower in nitroglycerin, but not significant compared to labetalol (P-value=0.063). Kim et al. stated that the occurrence of asymptomatic spasms in patients is more common.<sup>17</sup> The study by Hizoh et al. showed that there was no difference between intra-arterial verapamil and placebo in terms of patients' pain.<sup>19</sup> But, in the study of Kiemeneij et al., the mean pain score in the group receiving verapamil+nitroglycerin was

#### Labetalol and Nitroglycerin in Radial Artery Spasm

significantly lower than the group without any medication  $(1.7\pm0.94 \text{ vs. } 2.08\pm1.07, \text{P-value}=0.03).^{24}$ 

Monma et al. explained that labetalol decreases heart rate and blood pressure in-vivo.<sup>25</sup> In our study, a significant non-serious blood pressure reduction has been seen in the labetalol group (P-value<0.001). But, no significant heart rate change has been observed in both groups (P-value=0.689). Hoskins et al. study explained that labetalol causes a significant drop in blood pressure and heart rate. Although, contrary to the results of previous studies, there was no significant heart rate reduction in the labetalol recipient group of the present study.<sup>26,27</sup> Also, there was no evidence of adverse effects such as hematoma in our trial.

This research had some limitations. In the present study, we chose the intra-arterial dose of labetalol based on intravenous dosing, because no previous studies were found in this regard. On the other hand, due to the lack of a placebo group in this study, the estimation of RAS prevalence was not possible. In the current study, the pain score (VAS) was measured only at the end of the procedure. It was better to measure the VAS at the beginning of the catheterization, as well as at the end of procedure to examine or eliminate the effect of some factors such as anxiety before or during the procedure on the patients' pain severity, and incidence of RAS.

We believe that labetalol, as well as nitroglycerin, can be considered as one of the effective agents in order to decrease radial access consequences. Further studies are highly recommended to determine labetalol efficacy and its appropriate dosing in preventing of RAS.

#### Conclusion

The present study showed that labetalol increased radial artery size and facilitated manipulation during the procedure. The rate of spasm immediately after vasodilator injection was lowered in labetalol group compared to nitroglycerin. However, total incidence of spasm was higher in patients receiving labetalol. Our results presented that labetalol like nitroglycerin could be effective in reducing the pain intensity in transradial access procedures. In addition, administration of intra-arterial labetalol did not have any adverse or life-threatening effect on the hemodynamic state of the patients.

## **Ethical Issues**

This study was approved by the institutional review board of the Mazandaran Heart Centre and Ethics Committee of Mazandaran University of Medical Sciences [IR. MAZUMS.REC.1397.158] [IRCT20151109024975N11]. Written informed consent was obtained from all patients.

## **Data Sharing**

Applicants can obtain data by contacting the corresponding author.

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## **Conflict of Interests**

The authors declared that there is no conflict of interest in this study.

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