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ORIGINAL ARTICLE

Influence of remote ischemic conditioning on radial artery occlusion

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Abstract
This study aimed to explore the influence of remote ischemic conditioning (RIC) on radial artery occlusion (RAO) and distinguish the risk factors for RAO. A total of 640 consecutive patients who prospectively underwent transradial artery coronary angiography (TRACA) (322 patients received RIC before TRACA) were enrolled. RIC was not performed in 318 patients. RAO was estimated using Doppler ultrasonography after the procedure. Patients were divided into two groups according to the protocol of RIC: RIC and non-RIC. The rate of RAO was significantly lower in the RIC group than in the non-RIC group. Patients were divided into two groups according to the patency of radial artery: radial artery patency (RAP) and RAO. The radial artery diameter was significantly narrower in the RAO group (2.31 ± 0.53) than in the RAP group (2.59 ± 0.47). The rate of applying β-blocker was significantly higher in the RAP group (69%) than in the RAO group (41%). The rate of applying trimetazidine was significantly higher in the RAP group (49.1%) than in the RAO group (17.6%). The multiple logistic regression analysis using radial artery diameter, RIC, β-blocker, and trimetazidine treatments revealed that small radial artery diameter, lack of β-blockers, and RIC were independent predictors of RAO. RIC might help in improving the rate of RAO. The multiple logistic regression analysis showed that the lack of β-blockers, RIC, and small radial artery diameter were independent predictors of RAO.

Keywords Radial artery occlusion · Remote ischemic conditioning · Transradial artery coronary angiography

Introduction

The use of transradial artery coronary angiography (TRACA) for diagnosis and establishing treatment strategies for atherosclerotic coronary artery disease is gaining more popularity due to its lower incidence of access site complications, better patient acceptance, shorter durations of hospitalization, and lower direct costs compared with transfemoral approach [1–6]. However, TRACA still causes site-related complications. Radial artery occlusion (RAO), which is one of the most important complications, is quiescent owing to the dual vascular supply of hands from the palmar arch. It limits the future use of radial artery as an access site for coronary intervention or as a conduit for coronary bypass grafting or fistula formation in hemodialysis patients. Therefore, it is important to prevent the occurrence of adverse events distinguishing and avoiding its risk factors and increasing profitable factors.

The development of RAO after TRACA is thought to occur through two main mechanisms: development of thrombus and intimal hyperplasia. The process of TRACA may lead to endothelial trauma and result in radial endothelial and vascular smooth muscle cell dysfunction expressed as the reduction in flow-mediated dilatation [7, 8]. Trauma to the endothelium may be vital in the development of thrombus and intimal hyperplasia.

The protective effect of remote ischemic conditioning (RIC) induced by simply inflating and deflating a blood pressure cuff placed on the limb (arm or leg) is a hot topic in recent years. It is reported in a growing number of public studies and meta-analyzes [9–12]. The protective mechanisms of RIC involved humoral and neuronal factors activated by RIC, which were transferred to the target organ from the remote site of stimulus [13–15]. The number of protective factors activated by ischemic conditioning was much higher at the transient ischemic site. In addition, they first acted at the nearest site, although the specific protective factors involved in this have not been clarified.

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In view of these observations, a hypothesis was proposed that RIC performed before TRACA might improve the rate of RAO. Therefore, this study was performed to observe the effect of RIC on RAO and distinguish the risk factors for RAO.

Materials and methods

Patient population

A total of 755 patients who prospectively underwent elective TRACA between September 2017 and April 2018 were enrolled. Ultimately, 322 patients underwent RIC randomly before TRACA, and 318 patients did not undergo RIC. Further, 115 patients were excluded owing to pathological Allen tests, not completing four times of RIC, changing the access site of coronary angiography, and prior radial intervention. We rolled consecutive patients who underwent coronary angiography. Patients were divided into two groups according their admission number. If patient's admission number was the odd number, the patient was grouped into RIC. If it was the even number, the patient was grouped into non-RIC.

The study conformed to the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Ethical Review Board of Jinan Central Hospital. All patients were given their informed consent in the study.

Protocol of RIC and Doppler ultrasound of the radial arteries

RIC was performed by placing a standard blood pressure cuff on the upper arm, which was the access site of coronary intervention. The blood pressure cuff was inflated to 200 mmHg and left inflated at this pressure for 5 min. The cuff was then completely deflated and left for 5 min. This cycle was repeated four times so that the total duration of the intervention was 40 min. RIC was completed before the patients went to the catheter room. Interval between RIC and coronary angiography was less than 1.5 h. The patients who did not complete RIC were excluded.

Radial artery ultrasound was routinely performed before RIC and on the second day after TRACA. The diameters of radial arteries measured at the segment 1-cm distal to the radial styloid process were recorded in 2D images before RIC with ultrasound. The patency of radial arteries was assessed by checking the blood flow with color Doppler ultrasound s within 24 h after TRACA.

Coronary angiography

A 6F catheter was used during coronary angiography, which was routinely performed via the right radial artery. Physicians who managed PCI did not know which patients underwent RIC. Patients who underwent the procedure via the femoral or ulnar artery were excluded from the study. Before the procedure, all the patients underwent the Allen test. The patency of radial arteries was tested, and the patients received standard antiplatelet treatments (acetylsalicylic acid and clopidogrel or ticagrelor) in loading doses. Heparin dose was calculated according to the weight of patients undergoing PCI, and at least 3000 IU was used. Radial sheaths were removed just after the procedure. Compression was performed with a conventional hemostasis plastic band, and it was loosened by one circle almost every 1.5 h after the procedure until the plastic band was completely loosened.

The influencing factors, including the history of hypertension and diabetes, levels of low-density lipoprotein and triglyceride, and perioperative medications of each patient were recorded.

Statistics

Statistical analyzes were performed using SPSS 23.0 (SPSS Inc, IL, USA). Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were expressed as numbers (percentages). A multiple logistic regression analysis was performed to identify the influencing factors for RAO. Continuous variables were compared using the Mann–Whitney *U* test. Differences between categorical variables were examined using the Chi-square or Fisher's exact test. A P value < 0.05 was considered statistically significant.

Results

Demographic and clinical features of study groups

The patients were divided into two groups according to the protocol of RIC: RIC and non-RIC. Table 1 summarizes the demographic and clinical features of these two groups. The rate of RAO was significantly lower in the RIC than in the non-RIC group (RIC 0.93% vs non-RIC 4.4%, $P = 0.006 < 0.05$).

The patients were divided into two groups according to the patency of radial artery estimated after the procedure by Doppler ultrasound examination: radial artery patency (RAP) and RAO. Table 2 summarizes the demographic

Table 1 Patient characteristics in terms of RIC

	RIC ($n = 322$)	Non-RIC ($n = 318$)	*P*
Sex (male), *n* (%)	173 (54)	165 (52)	0.641
Age, year	62.85 ± 9.584	63.39 ± 9.635	0.484
Smoking, *n* (%)	112 (35)	126 (40)	0.205
Hypertension, *n* (%)	201 (62)	206 (65)	0.535
Diabetes, *n* (%)	97 (30.12)	95 (29.87)	0.945
Triglyceride, mmol/L	1.55 ± 1.2	1.62 ± 1.4	0.507
Low-density lipoprotein, mmol/L	2.76 ± 0.98	2.80 ± 0.94	0.620
Stain, *n* (%)	322 (100)	318 (100)	1.000
Clopidogrel, *n* (%)	148 (46)	134 (42)	0.330
β-Blocker, *n* (%)	225 (70)	213 (67)	0.431
Calcium antagonist, *n* (%)	135 (42)	125 (39	0.500
Renin–angiotensin system inhibitor, *n* (%)	172 (53)	173 (54)	0.802
Nitrate esters, *n* (%)	63 (20)	72 (23)	0.340
Nicorandil, *n* (%)	2 (0.6)	6 (1.9)	0.150
Trimetazidine, *n* (%)	165 (51)	144 (45)	0.131
Postprocedural anticoagulation, *n* (%)	12 (3.7)	13 (4.1)	0.814
Procedural time, min	36 ± 24	38 ± 25	0.338
Dose of heparin during the procedure, IU	4992 ± 1876	5261 ± 1869	0.070
Inner diameter of radial artery, mm	2.59 ± 0.48	2.57 ± 0.46	0.570
RAO, *n* (%)	3 (0.93)	14 (4.4)	0.006

RAO radial artery occlusion, *RIC* remote ischemic conditioning

Table 2 Patient characteristics in terms of RAO

	RAO ($n = 17$)	Non-RAO ($n = 623$)	*P*
Sex (male), *n* (%)	5 (29)	333 (54)	0.079
Age, year	63 ± 1	63 ± 10	0.998
Smoking, *n* (%)	3 (18)	235 (38)	0.091
Hypertension, *n* (%)	11 (65)	396 (64)	0.923
Diabetes, *n* (%)	3 (18)	189 (30)	0.260
Triglyceride, mmol/L	1.64 ± 1.65	1.59 ± 1.32	0.875
Low-density lipoprotein, mmol/L	2.73 ± 0.87	2.78 ± 0.97	0.812
Clopidogrel, *n* (%)	7 (41)	275 (44)	0.808
Stain, *n* (%)	17 (100)	623 (100)	1.000
β-blocker, *n* (%)	7 (41)	431 (69)	0.014
Renin–angiotensin system inhibitor, *n* (%)	7 (41)	338 (54)	0.286
Calcium antagonist, *n* (%)	8 (47)	252 (40)	0.584
Nitrate esters, *n* (%)	2 (12)	133 (21)	0.339
Trimetazidine, *n* (%)	3 (17.6)	306 (49.1)	0.010
Nicorandil, *n* (%)	0 (0)	8 (1.3)	0.638
Postprocedural anticoagulation, *n* (%)	0 (0)	25 (4)	1.000
Procedural time, min	34 ± 27	37 ± 24	0.578
Dose of heparin, IU	4941 ± 1713	5131 ± 1881	0.681
Inner diameter of radial artery, mm	2.31 ± 0.53	2.59 ± 0.47	0.015
RIC, *n* (%)	3 (17.6)	319 (51.2)	0.006

RAO radial artery occlusion, *RIC* remote ischemic conditioning

and clinical characteristics of these two groups. As shown in Table 2, the radial artery diameter was significantly ($P = 0.015 < 0.05$) narrower in the RAO group (2.31 ± 0.53) than in the RAP group (2.59 ± 0.47). The use of β-blocker and trimetazidine during the perioperative period was significantly different in the two groups. The rate of applying

β-blockers was significantly higher ($P = 0.014 < 0.05$) in the RAP group (69%) than in the RAO group (41%). The rate of applying trimetazidine was significantly ($P = 0.01$) higher in the RAP group (49.1%) than in the RAO group (17.6%).

Independent predictive factors for RAO

The multiple logistic regression analysis using radial artery diameter, RIC, β-blockers, and trimetazidine treatment revealed that small radial artery diameter, lack of β-blockers, and RIC were independent predictive factors for RAO (Table 3).

Discussion

Although RAO largely remains silent in the clinic and rarely results in ischemia, it limits the use of radial artery in future operations. Many factors probably affect the incidence of RAO, such as patient weight, radial artery diameter, ratio between radial artery diameter and sheath size, repeated procedures, prolonged cannulation time, compression method, continuous compression time, and heparin dose [16]. The present study found that small radial artery diameter, lack of β-blockers, and RIC were independent predictive factors for RAO.

A large number of studies reported that RIC could support protection against ischemia–reperfusion injury. The meta-analysis by Elbadawi concluded that RIC might improve cardiovascular outcomes in patients with ST-segment elevation myocardial infarction who underwent primary coronary intervention evidenced by reduced release of biomarkers, major adverse cardiac and cerebrovascular events, and better ST-segment resolution [9]. The study by Kanoria demonstrated that RIC had the potential to reduce liver injury following hepatectomy [10]. Zhou stated that RIC was a useful strategy for minimizing cardiopulmonary bypass-induced organ injuries in patients undergoing cardiopulmonary bypass surgery [11]. The study by Balcı demonstrated that RIC decreased renal ischemia–reperfusion injury significantly [12]. The study by Kitagawa showed that RIC could support brain protection by reducing infarct size during cerebral ischemia through enhanced collateral circulation in murine focal cerebral ischemia [17].

Ischemic conditioning is an endogenous protective strategy. PCI can lead to endothelial dysfunction [7], which is one of the important reasons for RAO. The study by Manchuroy confirmed that RIC could improve the endothelial function of the brachial artery. The improvement in endothelial function could remain constant for at least a week [18]. The study by Pedersen found that RIC could prevent systemic platelet activation associated with ischemia–reperfusion injury in humans [19]. It also discovered that RIC modified the function of human neutrophils by modifying inflammatory gene expression [20–22]. Accordingly, RIC might be beneficial in decreasing the occurrence of RAO, as found in the present study.

The use of a small-diameter guide catheter reduced the injury to the radial artery and resulted in fewer instances of RAO [23]. Rashid et al performed a pooled analysis to study the effect of various sizes (3, 4, 5, 6, 7, and 8 Fr) of catheters on the incidence of RAO. They observed that RAO rates increased with the increasing size of guide catheter systems used [24]. The radial artery diameter and sheath-to-artery size ratio were found to be associated with better RAO outcomes [25, 26]. In the present study, 6-Fr sheath guide catheters were used. The RAO group was found to have relatively smaller radial artery diameters compared with the non-RAO group. Small radial artery diameter was a significant independent predictor of RAO.

β-blockers can reverse the neurohormonal effects of the sympathetic nervous system and serve as a primary pharmacological treatment for chronic heart disease, inducing prognostic and symptomatic benefits. Specifically, β-blockers have been shown to prolong survival by preventing arrhythmia, improving chronic heart diseases symptoms and left ventricular ejection fraction, and controlling ventricular rate [27]. The present study found that applying β-blockers might reduce the rate of RAO. β-blockers were usually applied to patients when their heart rates were more than 70 times every minute and their blood pressure was higher than 100/60 mmHg. Therefore, a relatively higher heart rate and a higher blood velocity in the radial artery help in decreasing RAO rates.

Trimetazidine decreases the use of free fatty acids for energy production by inhibiting the activity of mitochondrial 3-ketoacyl coenzyme A thiolase in beta-oxidation, thus shifting metabolism toward glucose [28]. Besides metabolic effects, trimetazidine was previously shown to have nonmetabolic effects such as inhibition of inflammatory response, improvement in endothelial dysfunction, and reduction of oxidative stress [29, 30]. A previous study indicated that trimetazidine protected against the loss of flow-mediated dilatation after transradial cardiac catheterization [31]. It also had some potential capability

Table 3 Independent predictors of RAO

Variable	Odds ratio	*P*	95% confidence interval
β-blocker	2.893	0.04	1.051–7.963
Inner diameter of radial artery	0.242	0.018	0.075–0.787
RIC	4.024	0.033	1.116–14.509

RAO radial artery occlusion, *RIC* remote ischemic conditioning

to inhibit intimal hyperplasia by inhibiting NADPH oxidase activation with the subsequent inhibition of NF-B activation [32, 33]. However, trimetazidine had no influence on RAO in the present study.

RIC was performed on contralateral arm or lower limb in other studies, and they found the protective effect of RIC on organs and tissues. In our present study, we conducted the same arm for RIC and coronary angiography, we discovered RIC could help to reduce incidence of RAO. Many studies suggested that remote ischemic preconditioning and remote ischemic postconditioning shared similar, or common mechanisms protecting organs [34, 35]. RIC on contralateral arm and lower limb have similar protection effect on organs [9]. RIC on contralateral arm or lower limb may share the similar mechanisms with RIC on the same arm [13, 14]. In this view, the same discovery may be seen by RIC on the contralateral arm or lower limb. However, protective mechanism against RAO is not quite clear. Therefore, large randomized controlled studies are still needed in the future to validate the findings and to study mechanisms of the findings.

The rate of RAO within 24 h is up to 7.7% [24]. In the present study, the rate of RAO in patients undergoing RIC was 0.93% and not undergoing RIC was 4.4%, respectively. The values were obviously lower, which might be due to the strategies used during the perioperative period, an experienced team of surgeons, abundant antiplatelet medications, effective anticoagulation medications (at least 3000 IU), relatively shorter compression time, relatively larger diameter of the radial artery (diameter compared with that in another study [36]), and application of RIC and standard medical treatments.

Limitation of the study

The limitation of the study was that the patients were consecutively enrolled, but not completely randomized. However, the number and characteristic of patients were balanced. A large randomized controlled study is still needed in the future to validate the findings and to study mechanisms of the findings.

Conclusions

Remote ischemic conditioning might be beneficial in improving the rate of RAO. The multiple logistic regression analysis showed that the lack of β-blockers, RIC, and small radial artery diameter were independent predictors of RAO.

Compliance with ethical standards

Conflict of interest All the authors have no funding, financial relationships, or conflicts of interest to disclose.

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