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To reverse or not to reverse the radial artery in coronary artery bypass graft surgery? Histopathologic concerns and media thickness

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ABSTRACT

Background and aims: Radial artery (RA) is a popular coronary artery bypass grafting (CABG) conduit. The challenging issue is vasospasm. A few studies are available on histopathological differences between RA's proximal and distal ends. This study aims to compare histopathological features of the proximal and distal end of RA to find the best technique for anastomosis.

Methods: In this matched case-control study, 80 patients were included who underwent CABG and used RA as a graft. Ten subjects were excluded. RA was harvested by open technique, and a cocktail of Papaverine, Verapamil, and Nitroglycerine was frequently applied topically. One centimeter of proximal and distal ends of the RA was evaluated considering its Histopathology. Clinical signs of RA graft vasospasm were monitored from harvesting until the post-operative period. Intima, media, and intima-media thickness (IMT) index were compared between the two cohorts.

Results: Vasospasm occurred in 1.41% of patients. The mean intimal thickness in the proximal and distal ends were, respectively, 0.20 (standard deviation [SD] 0.17 mm) vs. 0.31 (SD 0.18 mm) ($p < 0.001$). The mean media thickness in the distal end was higher than the proximal end (0.98 [SD 0.36] vs. 1.09 [SD 0.37], $p = 0.004$). IMT index of the proximal and distal ends showed a statistically significant difference (0.22 [SD 0.17] vs. 0.31 [SD 0.19]) ($p < 0.001$).

Conclusion: The overall incidence rate of vasospasm in our study is comparable with other studies using the same cocktail. Proximal RA has a relatively lower medial thickness compared to the distal part, which may induce less vasospasm in CABG patients.

1. Introduction

Coronary artery bypass graft surgery (CABG) is the gold standard treatment of severe coronary artery disease [1]. As more severe coronary artery diseases are accepted for operation recently, more conduits are needed during the operation [2]. Moreover, the

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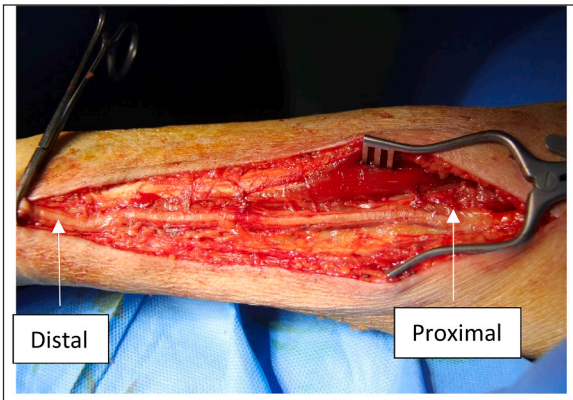
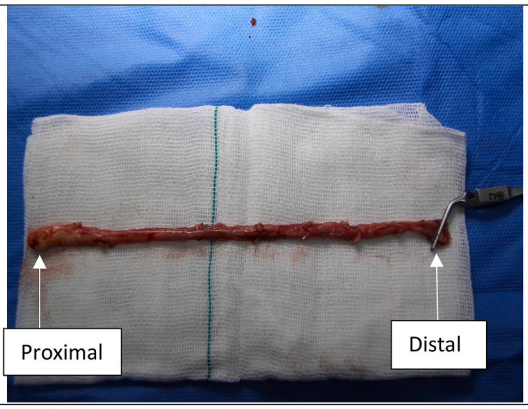
patency rate of the grafts plays a significant role in choosing the conduits. Between the most famous conduits, namely internal mammary artery (IMA), radial artery (RA), and saphenous vein graft (SVG), the best patency rate belongs to IMA.

Commonly, arterial grafts are perceived as superior to veins, with IMA exhibiting the highest patency rates [1,3].

Carpentier et al. first described RA as an arterial conduit in CABG in 1973. However, short-term angiography results for RA conduits



A- Radial artery (RA) dissection. As shown distal mark is on the wrist end.

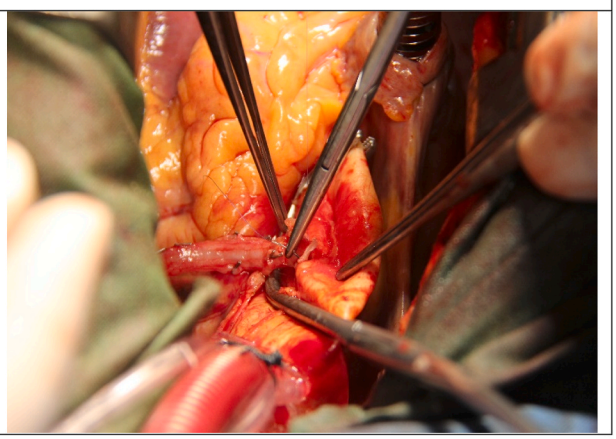


B- RA harvested. Bulldog is placed on distal end (Wrist end).RA is reversed from its anatomic position.

C- Administering a low-pressure cocktail of Papaverine, Verapamil, TNG mixed with blood intra-arterially via syringe to reveal any side branch bleeding.

D- The proximal end (Brachial end) of RA is speculated and prepared to anastomosis.

E- The proximal end (Brachial end) of RA is anastomosed to coronary artery.



F- The Distal end (Wrist end) of RA is anastomosing to Aorta.

Fig. 1. Intra operative surgical technique of RA harvest and anastomosis.

were discouraging [1,3]. Two decades later, Acar reused RA as a conduit, and his first series of patients showed a favorable patency rate, thus revitalizing RA as a conduit in CABG [3,4]. The benefits of RA conduits include easy harvesting technique, adequate length and inner diameter, and sustainable patency in the long term. Accordingly, RA has gradually become the second-best choice for arterial conduits following IMA [1,3,5,6].

RA has thick media and a sensitive endothelium, making it susceptible to spasms. There is a large body of literature regarding the pharmacological agents to reduce vasospasm from 35-50% to 0.3–10% [1,2,5,7–10]. Since 1992, calcium channel blockers have been used to reduce RA spasms [1,2,8]. Histopathologic and morphometric studies on RA have elucidated the association of its media thickness with vasospasm rate. To tackle this shortcoming, some studies have suggested discarding the distal end of RA. However, evidence of differences in histopathological characteristics between proximal and distal ends of RA is rare [11]. In our experience, the common practice is to use the RA in the reverse position because of its larger diameter in the proximal part.

The objective of this investigation is to conduct a comparative analysis of the histopathological characteristics of the media layer at both the proximal and distal ends of RA, serving as a proxy to assess the artery's inclination towards vasospasm.

2. Materials and methods

2.1. Site, population, and variables

This study is a matched case-control with peri-operative follow-up. Between June 2019 to November 2020, all patients who underwent CABG or CABG-valvular surgery at Milad Hospital (Isfahan, Iran) and utilized RA as a graft were enrolled. The ethics committee at Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.858) reviewed and approved the study's protocols. Written consent has been obtained from all of the participants. Participants consented to have their images published. A checklist consisting of 34 multiple-answer questions was designed for completion by the surgical team, intensive care unit (ICU) nurse, surgeon, and pathologist. The checklist variables included the demographic variables, history of smoking, diabetes mellitus (DM), hypertension (HTN), number of diseased coronary arteries, left main disease, congestive heart failure (CHF), RA graft site (obtuse marginal artery [OM 1, 2, or 3], diagonal artery, ramus artery, right coronary artery [RCA], right ventricular [RV] branch, posterior descending artery [PDA], posterior left ventricular artery [PLV]), left main stenosis status on the urgency of operation, intra-aortic balloon (IABP) pump use, incidence of peri-operative vasospasm of RA, length of hospital and/or ICU stay (days), disposition (alive/dead), and histopathological findings of the proximal and distal end of RA, including intima, media thickness, and intima-media index(Fraction of Intima to media). One surgeon did all of the surgeries with 30-years of experience. The surgical technique was the same among the patients.

2.2. Surgical technique

The non-dominant hand was used as the donor site. The Allen test was performed routinely prior to surgery by two surgeons. In case of a positive Allen test or previous neurological or skeletal disease, RA was not used. A full-length forearm skin incision (S-shaped) was made by a scalpel, followed by a dissection of subcutaneous fat and deep fascia over the Brachioradialis muscle to expose the RA. A light bulldog clamp was applied to the distal part, resulting in engorgement of RA. The artery was sharply dissected without using cautery to decrease neural damage. Metal clips were placed on both sides of the branches (Fig. 1(A)). The maximum RA length was dissected from one inch distal to the elbow crease to one inch proximal to the patient's wrist, and consequently, RA was harvested (a bulldog clamp marked the distal end) (Fig. 1(B)). The harvested RA was placed in a solution containing warm Papaverine (40 mg) and Verapamil with Tri-Nitro-Gelycerin (TNG) (5 mg) in 100^{cc} normal saline, and it was frequently sprayed on RA during the surgery. Before anastomosing, we administered a low-pressure cocktail of Papaverine, Verapamil, TNG mixed with blood intra-arterially via syringe to reveal any side branch bleeding (Fig. 1(C)).

The RA was reversed from the anatomic position: the proximal end (Brachial end) of RA was anastomosed to the coronary artery and the distal site (wrist end) to the aorta (Fig. 1(D,E,F)).

RA donor site hemostasis was performed carefully. The fascia was not closed to prevent compartment syndrome. Further, a loose elastic bandage was used to prevent hematoma. The incision site was inspected and examined frequently post-operatively concerning hematoma, infection, seroma, neurological, and vascular complications [2,3]. Clinical signs of RA graft vasospasm were monitored from harvesting until the post-operative period. At ICU, the spasm was detected by ST-T changes in continuous electrocardiogram (ECG) monitoring. If vasospasm occurred, bolus verapamil and TNG were administered intravenously (IV) until normalizing the ECG changes.

2.3. Histopathologic examination

The proximal and distal ends of RA were immersed in 10 % formalin and transferred to the pathology department (cut widths 1 cm). Specimens were placed in a tissue cassette. Tissue processing was done by 12 plates (formalin 10 %, alcohol [70, 80, 90, and 100%], Xylol, paraffin), and the cassette was placed in each plate for 1 h. Slides were taken by microtome instrument in 3 mm thickness. All sections were stained with Hematoxylin and eosin staining (H&E) for histological examinations. The slides were mounted. Intima, media thickness, and intima-media indices (IMT) were made with an optical microscope. Intima and media thickness were reported in millimeters (Figs. 2 and 3).

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY). The descriptive data were reported as mean with standard deviation (SD), absolute number, and percentages. We used paired sample T-test and one-way ANOVA to compare histological variables in matched patients. Two-sided P-values less than 0.05 was considered significant.

3. Results

A total of 80 patients were initially included in the study. However, ten patients were subsequently excluded due to unsuitable RA specimens or inadequate preparation of pathologic slides. As a result, the study group was confined to 70 patients, of which 55 were men (78.6 %). The mean age of men and women was 66.02 (SD 9.09) and 64. 64 (SD 8.9), respectively. The mean body mass index (BMI) was 26.6(SD 5.42). 54.3 % of patients had HTN. The most frequent procedure group was CABG (94.3 %). Thirteen cases underwent urgent CABG.

The most frequent site for RA grafts was OM1 (28,40 %). The mean bypass time was 89.89(SD 20.35) minutes. The mean Aortic cross-clamp time was 56.44 (SD 16.17) minutes. The median blood loss was 650(IQR 450–900 cc).

Ten subjects developed low cardiac output in the post-operative period and were treated with Intra-Aortic Balloon Pump (IABP). One patient experienced vasospasm which was during the harvest (1.41 %), and was managed with an intra-arterial injection of a cocktail of Papaverine, Verapamil, and TNG. One patient died in the post-op period who tested positive for COVID-19. Pre- and peri-operative descriptive characteristics of cases are shown in Tables 1 and 2.

The mean intimal thickness between the proximal and distal ends, respectively, were 0.20 (SD 0.17) and 0.31 (SD 0.18) ($p < 0.001$). Media thickness in the distal end was more than the proximal end (0.98 [SD 0.36] vs. 1.09 [SD 0.37], $p = 0.004$). The difference in IMT index between the proximal and distal end was statistically significant (0.22 [SD 0.17] vs. 0.31 [SD 0.19] mm, <0.001). Table 3 presents the results of histopathological investigations.

The RA histology analysis was further stratified by the presence of DM and HTN (Table 4).

4. Discussion

The demand for additional conduits in contemporary cardiac surgery is on the rise, and among them, the RA stands as a suitable choice. In order to decrease the rate of vasospasm, we hypothesized that reversing the radial artery and anastomosing the proximal end to the aorta leads to elevated patency rates. Our investigation aimed to compare the proximal and distal ends of the RA regarding the histopathological characteristics. Previous studies have shown that the rate of RA vasospasm during CABG varies between 0.3 and 10 % [2,5,10]. Comparably, we found the RA vasospasm to be 1.41 %.

The management of arterial vasospasm in CABG is a topic of continuous debate. Since the introduction of RA as a graft, many pharmacological agents have been administered to control this phenomenon [12]. In an *in vitro* study, which was done on 74 RA segments and 85 internal thoracic artery segments, it was shown that using Nicardipine and Nitroglycerine cocktail exhibited the best relaxant results [7]. In a randomized control trial on 131 subjects who underwent CABG with RA as a graft, the arterial flow was compared after using Verapamil versus Nicardipine, and it was concluded that the administration of topical Nicardipine was safe and effective [10]. A narrative review by Guo-Wei He et al. showed that using a combination of a calcium channel blocker and a topical nitric oxide (NO)-releasing agent such as TNG with liberal use of systemic calcium antagonist showed yielded favorable outcomes. It is concluded that frequent use of calcium channel blockers with TNG is applicable during CABG [8].

In this study, pre-operatively, we prescribed Diltiazem 30 mg TDS orally from the day before surgery. During the harvest, we continuously sprayed on RA with a solution of 40 mg Verapamil and 5 mg TNG in 100 cc normal saline. Before performing

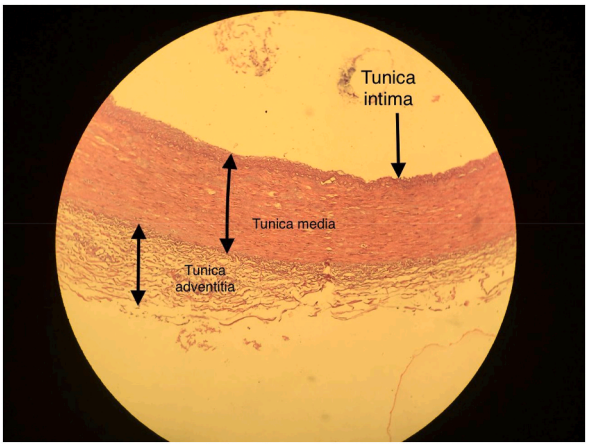


Fig. 2. Proximal end of the radial artery under an optical microscope.

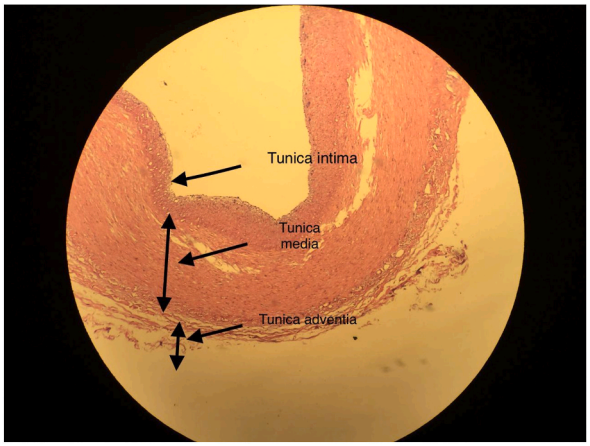


Fig. 3. Distal end of the radial artery under an optical microscope.

Table 1
Descriptive data of patients that Radial Artery used as a conduit.

		Frequency (N = 70)	Percent (%)
Gender	Men	55	78.6
	Women	15	21.4
Smoking	Never smoked	56	80
	Ex-smoker[1]	1	1.4
	Current smoker	13	18.6
Diabetes mellitus	Oral	21	30
	Insulin	2	2.9
	Oral + Insulin	3	4.3
Hypertension		38	54.3
Previous PCI[2]		9	12.9
Number of diseased coronary arteries	Two	4	5.7
	Three	66	94.3
Procedure group	CABG[3]	66	94.3
	CABG + valve	4	5.7
RA graft site on coronary	OM[4] 1	28	40
	OM 2	13	18.5
	Diagonal	10	14.3
	Ramus	7	10
	RCA[5]	4	5.7
	OM 3	2	2.9
	RV branch[6]	2	2.9
	PDA[7]	2	2.9
	PLV[8]	1	1.4
	Head of distal pouch	1	1.4
Left main disease		16	22.9
Urgency status of an operation	Elective	57	81.4
	Urgent	13	18.6
IABP[9]		10	1.4
Vasospasm in perioperative period		1	1.42
Status on discharge	Alive	69	98.58
	Dead	1	1.42

1-Ex-smoker: cessation of smoking from 6 months ago,2-percutaneous coronary intervention, 3-coronary artery bypass graft, 4-Obtus marginal, 5-Right coronary artery, 6-Right ventricular branch, 7-Posterior descending artery, 8-Posterior of left ventricle, 9- Intra- Aortic Balloon Pump,

anastomosis, we further administered Papaverine intra-arterially at a slow rate. However, other surgeons prefer applying Dobutamine and TNG cocktails during the CABG [2].

In this study, we observed the distal end showed a higher intimal thickness. Similarly, Chowdhury et al., in an observational study of 190 patients who underwent CABG, showed significant differences in intimal hyperplasia between the proximal vs. distal end of RA (0.12 vs. 0.89 mm). In that study, it was concluded the distal end should not be used in CABG [11].

A Doppler ultrasound study on 100 subjects who underwent CABG with RA graft demonstrated that intima thickness was more than the proximal [13], which was similar to our study. In contrast, in a histopathologic study, Ueyma et al. showed that the difference in intimal thickness between RA and internal thoracic artery in CABG was non-significant (0.18 vs. 0.26 mm). However, the proximal end was slightly larger than the distal [13,14].

Table 2
Descriptive data Pre-operative and peri-operative period.

	Min	Max	Mean	Std. Deviation
Ejection fraction	20	65	50.40	13.94
Weight (kg)	48	126	76.90	15.69
Bypass time (min)	56	172	89.89	20.35
Cross clamp time (min)	33	111	56.44	16.17
Hospital stay (day)	3	17	9.02	2.65
ICU stay (day)	1	10	3.60	1.66

Table 3
Histopathological preferences of the proximal and distal end of RA.

		Elbow	Wrist	P- value
Intima thickness	Minimum	0.03	0.02	<0.001
	Maximum	0.70	0.80	
	Mean	0.198	0.311	
	Std. deviation	0.1652	0.177	
Media thickness	Minimum	0.10	0.50	0.004
	Maximum	2	2	
	Mean	0.981	1.088	
	Std. deviation	0.363	0.371	
Intima-media index	Minimum	0.41	0.18	<0.001
	Maximum	0.75	1	
	Mean	0.215	0.307	
	Std. deviation	0.172	0.191	

Table 4
Histopathological preferences of the proximal and distal end of RA in DM and HTN.

			Mean	Std-deviation	P-value
Diabetes mellitus	Oral	P-intima	0.207	0.937	0.14
		D-intima	0.308	0.143	
		P-media	1.121	0.475	0.29
		D-media	1.161	0.429	
		P-IMT index	0.203	0.099	0.012
		D-IMT index	0.270	0.097	
	Insulin	P-intima	0.100	0	0.364
		D- intima	0.225	0.106	
		P-media	0.950	0.212	0.656
		D-media	1.100	0.565	
		P-IMT index	0.107	0.024	0.063
		D-IMT index	0.207	0.010	
	Oral + insulin	P-intima	0.600	0.141	0.795
		D- intima	0.675	0.176	
		P-media	1	0.282	0.500
		D-media	0.975	0.247	
		P-IMT index	0.604	0.029	0.671
		D-IMT index	0.739	0.368	
Hypertension		P-intima	0.24	0.182	0.002
		D-intima	0.337	0.199	
		P-media	1.000	0.291	0.851
		D-media	1.12	0.356	
		P-IMT index	0.252	0.190	0.005
		D-IMT index	0.332	0.241	

The intima-media thickness (IMT) index is a prognostic factor for cardiovascular events and graft patency. Many studies show that after CABG, the RA IMT index decreases gradually [11,15–18]. We found that the IMT index was higher in the distal end compared to the proximal. Eklund et al. followed up the IMT index of RA in 133 angiography candidates using myocardial perfusion scintigraphy. Similar to our findings, they found that in a three-year follow-up, the IMT index decreased (0.34 vs. 0.31), suggesting the IMT index is a prognostic factor for cardiovascular events [15].

In Chowdhury et al.'s study, the difference in IMT index between the proximal (0.12) and the distal end (0.89 ± 0.22) was statistically significant, suggesting that the great majority of intimal hyperplasia mainly affects the distal portion, and it should be discarded when performing CABG [11]. According to our results, the radial artery should be reversed before anastomosis in order to have

less intimal thickness and IMT index in coronary anastomosis.

RA is a muscular graft. The higher the media thickness, the easier the anastomosis for surgeons. But the rate of vasospasm increases [3,12].

In this study, media thickness in the distal end is higher than the proximal end. In the same study, which examined 100 patients who had RA as a graft during CABG, Doppler was used to determine the morphometric and histopathologic RA. Media thickness was higher in the distal end in comparison with the proximal end (0.142 vs. 0.213). Atherosclerotic disease is higher in the distal end. It is concluded that the distal end of RA is grafted to the aorta, and the better part should be anastomosed to the proximal part [13]. Some surgeons prefer anastomosing RA in T-shaped IMA or vein [12]. Both coronary and RA are muscular arteries. In order to decrease the rate of vasospasm, we hypothesized that reversing the radial artery and anastomosing the distal end to the aorta is the suitable method.

DM and HTN have been shown to affect atherosclerosis. When stratified for DM (patients on oral blood sugar lowering medications, insulin, or both), we found no significant difference between the two ends regarding intima/media thickness and IMT index. However, the mean thickness of the intima in oral and insulin groups was slightly higher compared with either oral or insulin groups. In Mete Gursoy. et al. study examining the distal RA of 36 subjects, it was shown that poor glycemic control was associated with a higher index of atherosclerotic RA [19]. We hypothesized that in diabetic patients with poor glycemic control, RA should be reversed. Nevertheless, we propose conducting further studies specifically focusing on diabetic patients.

In our study, hypertensive patients with uncontrolled blood pressure exhibited significantly higher media thickness and IMT index values. As such, we advocate for further investigations with larger sample sizes, focusing on hypertensive patients undergoing CABG to gain a comprehensive understanding of the implications of HTN in this context.

The present study encountered a limitation due to the impact of the COVID-19 pandemic, which resulted in a reduced number of available subjects. Therefore, we propose future research endeavors with larger population sizes to overcome this constraint and further investigate the pharmacological and histopathological aspects related to HTN and DM.

5. Conclusion

Our findings suggest that the radial artery should be reversed when anastomosing to the coronary artery to use better histology of RA in order to have less intima/media thickness and IMT index.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author (Pouya MMSadeghi). The data are not publicly available due to restrictions which their containing information could compromise the privacy of research participants.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Pouya Mir Mohammad Sadeghi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition, Resources, Supervision. **Mohsen Mir Mohammad Sadeghi:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Maryam Derakhshan:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Amir Mir Mohammad Sadeghi:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Amir Hossein kazemian:** Conceptualization, Data curation, Methodology, Resources, Writing – original draft. **Ali Abbasvand:** Conceptualization, Data curation, Formal analysis, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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