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Prophylactic intra-arterial injection of lidocaine: a novel strategy to prevent endovascular embolization-induced trigeminocardiac reflex

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ABSTRACT

Background Trigeminocardiac reflex (TCR) is a brainstem reflex that can lead to hemodynamic instability manifested as bradycardia, decrease/increase of mean arterial pressure (MAP) and, in the worst case scenario, asystole during surgery. The effective intraoperative management of recurrent and profound TCR has yet to be established. This randomized paired study was performed to identify the effect of a prophylactic intra-arterial injection of lidocaine to prevent TCR caused by Onyx embolization during cerebrovascular intervention surgery.

Methods A total of 136 patients who received Onyx embolization under general anesthesia were assigned to a control group pretreated with intra-arterial saline injection or a lidocaine group pretreated with an intra-arterial injection of 20 mg lidocaine. Heart rate (HR) and MAP were closely monitored during the embolization procedures and the incidence of TCR, mainly characterized by a decrease in HR of ≥20%, and perioperative adverse events was recorded.

Results During dimethyl sulfoxide (DMSO)/Onyx injection, HR was much slower in the control group than in the lidocaine group ($p<0.05$). TCR occurred in 12 patients (17.6%) in the control group (cardiac arrest in 3 patients) with decreased (7 cases) or increased (5 cases) MAP, whereas no TCR was observed in the lidocaine group. Notably, most TCR episodes occurred in patients with dural arteriovenous fistula and middle meningeal artery being affected. The composite adverse events were significantly higher in the control group than in the lidocaine group ($p<0.05$).

Conclusion This prospective study shows that a prophylactic intra-arterial injection of 20 mg lidocaine could be recommended as a novel strategy to effectively and safely prevent TCR during endovascular embolization.

Trigeminocardiac reflex (TCR) is a unique brainstem reflex which manifests as the sudden onset of hemodynamic perturbation in heart rate and blood pressure as a result of stimulation of any branches of the trigeminal nerve.[1] TCR has been described during intracranial, maxillofacial, ophthalmic surgery, and is often observed in the endovascular treatment of intracranial dural arteriovenous fistula (DAVF) or carotid–cavernous fistula (CCF) and radiofrequency lesioning of the trigeminal ganglion.[2]

With the development of neurointerventional technology, Onyx embolization is now a well-established technique for the treatment of cerebrovascular malformation.[3] However, TCR is one of the most reported complications and is commonly seen during cerebrovascular embolization with Onyx.[4–6] The occurrence of TCR is unpredictable without a clear detection index, and to date there is no consensus or guidelines to direct the treatment and prevention of intravascular manipulation-induced TCR. Once the TCR episode occurs, it may lead to catastrophic cardiovascular complications and pose an immediate threat to life.[7 8] Therefore, it is crucial to evaluate the potential risk factors of TCR and to adopt proper measures to block TCR-related severe hemodynamic perturbations during endovascular embolization.

Previous studies have demonstrated the efficacy of topical local anesthetic and local anesthetic nerve blocks in preventing TCR.[9–12] However, there has been no systematic research on the use of lidocaine for TCR caused by mechanical stimulation of the trigeminal nerve during Onyx embolization. Two recent case reports by Coleman *et al*[13] and our group[14] showed that a prophylactic intra-arterial injection of lidocaine was able to blunt TCR during endovascular treatment of CCF and DAVF.

We therefore designed a prospective study to investigate whether a prophylactic intra-arterial injection of lidocaine could be considered as a novel strategy to prevent the occurrence of TCR at the time of dimethyl sulfoxide (DMSO)/Onyx injection during cerebrovascular embolization. To our knowledge, this is the first randomized controlled trial to explore the efficacy of intra-arterial lidocaine in blunting TCR during endovascular neurosurgery.

MATERIALS AND METHODS

Patients

This was an investigator-initiated prospective double-blind randomized and paired trial conducted in The First Affiliated Hospital of Nanjing Medical University from June 2020 to July 2021 (chictr.org.cn ChiCTR2000034503; July 7, 2020). The study was approved by the ethics committee (The First Affiliated Hospital of Nanjing Medical University/Jiangsu Province Hospital, China, June 19, 2020). Written informed consent was obtained from all participating patients before inclusion in the study. An independent data and safety monitoring board

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oversaw the conduct of the study and reviewed blinded safety data.

All patients were aged >18 years with an arteriovenous malformation (AVM), DAVF or CCF. They were planned to undergo Onyx embolization under general anesthesia. Participants were screened and recruited by study staff who evaluated patient eligibility, obtained informed consent, and enrolled the participants. Exclusion criteria included known allergies to any of the drugs used for anesthesia or to any of their excipients, severe cardiovascular disease and urgent surgery. Patients with preoperative confusion and communication difficulties were also excluded.

Study design

Randomization and interventions

Patients were matched into 68 pairs based on their diagnosis and randomized in a 1:1 ratio to either the control group pretreated with intra-arterial saline or the lidocaine group pretreated with intra-arterial injection of 20 mg lidocaine. Randomization was centralized and computer generated, and each patient was given a unique randomization number. All operation procedures were performed by the same neurosurgeon who was unaware of the grouping during intra-arterial injection and the Onyx embolization. Treatment assignments were concealed from patients, non-medical research staff, the statistician, and the data and safety monitoring committee.

Operation and anesthesia procedures

All procedures were performed under general anesthesia and systematic heparinization. The surgeon punctured the right femoral artery generally, a Neuron Max guide catheter was placed in the proximal vessel and an Apollo microcatheter was advanced to the relevant artery using an intermediate catheter for support under C-arm fluoroscopic guidance. A microcatheter injection was performed to confirm the fistulous point. When all catheters were in a stable position, embolization of the fistula proceeded. Patients in the lidocaine group received an intra-arterial injection of 1 mL 2% lidocaine within 1 min, while patients in the control group were continuously injected with 1 mL normal saline at the same rate. The nurse prepared the saline or lidocaine solution accordingly and then handed the unlabeled solution to the surgeon for the intra-arterial injection. Following lidocaine or normal saline injection, DMSO and Onyx were injected at 0.2 mL/min successively. The procedure was considered successful when multiple DSA showed complete embolization of the target vessels.

A uniform anesthesia protocol was used for anesthesia induction and maintenance. Intraoperative monitoring included peripheral capillary oxygen saturation, electrocardiography, heart rate (HR) and invasive arterial blood. The depth of anesthesia was guided by the Bispectral Index (BIS) which was kept at 40–50 to prevent intraoperative awareness. The intraoperative hemodynamic changes were closely monitored. If the heart rate fell to <40 bpm, 0.5 mg of atropine was injected intravenously.

Variables and outcomes

The primary outcomes were HR and mean arterial pressure (MAP). These variables were monitored continuously and the minimum HR and corresponding MAP were recorded at the following time points: 5 min before anesthetic induction (T1), 1 min before lidocaine/saline injection (T2), at the time of lidocaine/saline injection (T3), 1 min before DMSO/Onyx injection (T4), at the time of DMSO/Onyx injection (T5) and at the end of the embolization procedure (T6). In addition, the incidence of TCR at T5 was recorded.

For the purposes of this study, TCR was defined as the sudden onset of bradycardia triggered by stimulation of the trigeminal nerve and its anatomic branches. The bradycardia is characterized by a reduction in HR ≥20% from the baseline. Change in MAP is an optional criterion for the definition of TCR,[15 16] but is not included as part of the TCR definition in this study. TCR type was defined according to the new classification scheme according to the onset of HR reduction: type IVa is defined as HR reduction before change in MAP and type IVb is classified as HR reduction following change in MAP.[17] The incidence of adverse events was also recorded including TCR episode, heart arrest, dizziness, postoperative nausea and vomiting, muscle weakness, and any other severe unexpected events (eg, aphasia, hypopsia) during the operation and within the first 24 hours following the operation.

Statistical analysis

To increase the quality of data analyses, each set of data was tested for normal distribution (D'Agostino and Pearson omnibus normality test) and for homogeneity of variances (Levene's test) before statistical analyses. To detect differences between the two groups, a paired t-test (paired, normal data) with Welch's correction in case of unequal variances, a Mann–Whitney test (unpaired, non-normal data) or a Wilcoxon matched-pairs signed rank test (paired, non-normal data) was used. Multiple comparisons were analyzed by repeated measures ANOVA with appropriate correction. Categorical variables in different groups were analyzed with a Pearson's χ^2 test or with Bonferroni correction for alpha inflation and the Monte Carlo simulation method if the expected frequency was lower than 5.

Statistical analyses were performed using IBM SPSS Statistics (Version 23, IBM SPSS, Chicago, Illinois, USA) and GraphPad Prism (Version 8, GraphPad Software, La Jolla, California, USA). A p value of <0.05 was considered to be statistically significant (two-sided for t-tests). Continuous variables are presented as mean±SD and categorical variables as number (%).

RESULTS

A total of 156 patients were approached for participation in the study (see online supplemental figure 1). Recruitment ended when the number of included subjects reached the calculated required sample size. Twenty patients were not enrolled or randomized for a variety of reasons including refusal to participate (n=6), unconsciousness (n=13), and atrial fibrillation (n=1). Thus, 136 subjects were enrolled in the study, randomized into pairs and allocated with 68 subjects in each group. Data from all 136 subjects were analyzed with no subjects lost during follow-up. The baseline demographic and clinical characteristics of the two groups were similar (table 1).

The HR and MAP in the two groups at the six time points are shown in figure 1. Compared with the control group, HR was significantly higher after a prophylactic intra-arterial injection of lidocaine at T5 (63.7±10.6 bpm vs 56.5±18.3 bpm, $p<0.05$). Lidocaine pretreatment also resulted in a higher MAP than in the control group at T5 (89.4±14.0 mmHg vs 79.1±25.1 mmHg, $p<0.05$) and T6 (90.0±8.6 mmHg vs 84.5±9.0 mmHg, $p<0.05$). Furthermore, we compared HR and MAP at T2 with those at other time points within the groups. In the control group, HR was slower at T5 (56.5±18.3 bpm) than at T2 (65.2±7.2 bpm) whereas, in the lidocaine group, HR did not show significant differences at all time points. However, there was no obvious difference in MAP within the control

Table 1 Baseline characteristics of patients

Characteristic	Control group (n=68)	Lidocaine group (n=68)	P value
Age, years	42.2±15.1	45.9±15.7	0.54
Male sex	40 (58.8)	43 (63.2)	0.60
BMI, kg/m^2	23.1±2.8	23.7±2.3	0.16
Comorbidities			
Hypertension	15 (22.1)	16 (23.5)	0.84
Diabetes	7 (10.3)	9 (13.2)	0.60
Bradycardia	8 (11.7)	7 (10.3)	0.78
History of cerebral hemorrhage	22 (32.3)	17 (25.0)	0.34
Protopathy			
AVM	32 (47.1)	32 (47.1)	1.00
DAVF	23 (33.8)	23 (33.8)	1.00
CCF	13 (19.1)	13 (19.1)	1.00
Supplying vessels			
Anterior cerebral artery	8 (11.8)	4 (5.9)	0.36
Middle cerebral artery	10 (14.7)	12 (17.6)	0.64
Posterior cerebral artery	7 (10.3)	6 (8.8)	0.77
Middle meningeal artery	17 (25.0)	16 (23.5)	0.84
Cavernous sinus	8 (11.8)	11 (16.2)	0.46
Ophthalmic artery	3 (4.4)	4 (5.9)	1.00
Other meningeal arteries	5 (7.4)	9 (13.2)	0.26
Other supplying vessels	10 (14.7)	6 (8.8)	0.29
Injected volume of Onyx (mL)	2.1 (1.6–2.6)	2.0 (1.5–2.7)	0.68

The data are presented as mean±SD for continuous variables, median (IQR) for abnormally distributed variables and frequency (%) for categorical variables.
AVM, arteriovenous malformation; BMI, body mass index; CCF, carotid–cavernous fistula; DAVF, dural arteriovenous fistula.

group, while MAP was higher at T5 (89.4±14.0 mmHg) and T6 (90.0±8.6 mmHg) compared with T2 (81.7±8.6 mmHg) in the lidocaine group.

As shown in table 2, 12 patients in the control group had a reduction in HR of >20%, a typical sign of TCR accompanied by either decreased (n=7) or increased (n=5) MAP. Furthermore, 16 patients solely experienced a 20% increase in MAP during the process of embolization (6 cases in the control group and 10 in the lidocaine group, p>0.05). Therefore, we consider

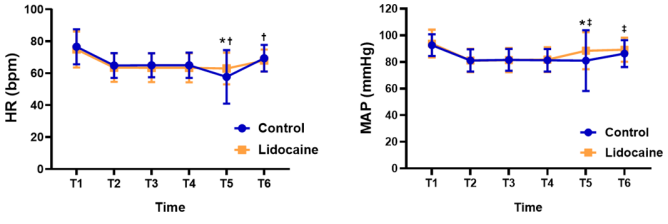

Figure 1 Changes in mean heart rate (HR) and mean arterial pressure (MAP) during the study. Data are shown for control and lidocaine groups at six time points during the study: T1, 5 min before anesthetic induction; T2, 1 min before lidocaine/saline injection; T3, at the time of lidocaine/saline injection; T4, 1 min before dimethyl sulfoxide (DMSO)/Onyx injection; T5, at the time of DMSO/Onyx injection; T6, at the end of the operation. *P<0.05, lidocaine group versus control group at certain time points; †p<0.05, T2 versus certain time points in the control group; ‡p<0.05, T2 versus certain time points in the lidocaine group.

a reduction in HR of >20% as a major manifestation of TCR in this study. On the other hand, no patient experienced TCR in the lidocaine group, which shows that intra-arterial pretreatment with lidocaine efficiently blocks TCR.

We further analyzed the anatomical site and affected cerebral blood vessels that might be associated with TCR. The incidence of TCR was mostly seen in patients with DAVF (75.0%) and those in whom the middle meningeal artery was the major vessel supplying the lesion site (58.3%). In patients who solely experienced a 20% increase in MAP during the process of embolization, there was no significant difference in DAVF and middle meningeal artery compared with other lesion sites and affected cerebral blood vessels. We therefore conclude that patients with DAVF and in whom the middle meningeal artery is the major supplying vessel are more likely to experience TCR with bradycardia and hypotension.

We detailed the occurrence, treatment, and classification in the 12 cases of TCR (see online supplemental table 1). There were three severe TCR cases presenting with cardiac arrest during Onyx embolization which were classified as IVa; two of them received immediate CPR/epinephrine and one was treated with atropine which resulted in a return to normal sinus rhythm shortly after the treatment. Notably, the two patients who required CPR suffered from DAVF with the middle meningeal artery affected. A further four TCR cases were classified as IVa, with the slowest HR <40 bpm prior to the reduction of MAP that required intravenous administration of atropine. The remaining IVb type TCR cases showed an increase in MAP followed by HR reduction without requiring any treatment.

Composite adverse events occurred in 29 of the 68 patients (42.6%) in the control group and in 13 of the 68 patients (19.1%) in the lidocaine group. The incidence of postoperative adverse events including dizziness, postoperative nausea and vomiting, muscle weakness and other events (aphasia, hypopsia and cerebral infarction) were similar in the two groups (table 3). There were three cases of severe cardiac arrest in the control group but none in the lidocaine group.

DISCUSSION

Endovascular embolization is a common procedure for treating cerebrovascular malformation due to its good outcomes and relatively low-risk profile.[18] However, the occurrence of TCR during treatment of abnormal vascular shunts may result in an intensive autonomic disturbance of the heart which manifests as a decrease in the HR, hypotension, arrhythmias and even cardiac arrest. In the present randomized controlled trial we found that a 20 mg lidocaine injection in the cerebral artery could effectively inhibit the incidence of TCR without central nervous side effects, showing that the prophylactic intra-arterial application of low-dose lidocaine is safe and effective in blocking endovascular embolization-induced TCR. Our result confirms the findings of two recent published case reports[13 14] in which 5–20 mg lidocaine prevented TCR during endovascular treatment in a patient with CCF and two patients with DAVF.

Preventive and therapeutic measures of TCR commonly recommended include cessation of surgical procedures once TCR occurs (such approach usually reverses the hemodynamic disturbance immediately), increasing the depth of anesthesia, application of anticholinergic agents such as atropine or vasoactive drugs (epinephrine) for refractory bradycardia and hypotension, and local anesthetic infiltration or nerve blocks. However, in some cases recurrent and profound bradycardia is resistant to pretreatment with anticholinergic agents and increased depth of anesthesia.[13] Topical anesthesia is not applicable for vascular

Table 2 Description of patients with significant hemodynamic fluctuations

	Total	Control group (n=68)	Lidocaine group (n=68)	P value	DAVF	Others	P value	Middle meningeal artery	Others	P value
HR decrease >20 (TCR)	12	12	0	<0.001	9 (75.0)	3 (25.0)	0.003	7 (58.3)	5 (41.7)	0.01
HR decrease >20% with MAP decrease	7	7	0	0.01	6 (85.7)	1 (14.3)	0.008	5 (71.4)	2 (28.6)	0.01
HR decrease >20% with MAP increase	5	5	0	0.07	3 (60.0)	2 (40.0)	0.43	2 (40.0)	3 (60.0)	0.79
Solely MAP decrease >20%	0	0	0	1.00	0	0	1.00	0	0	1.00
Solely MAP increase >20%	16	6	10	0.29	7 (43.8)	9 (56.2)	0.43	5 (31.3)	11 (68.7)	0.51

DAVF, dural arteriovenous fistula; HR, heart rate; MAP, mean arterial pressure; TCR, trigeminocardiac reflex.

embolization-induced TCR as the surgical manipulation is an interventional but not open surgery. Nerve block is also not feasible because it might cause intracranial hemorrhage and infection during cerebrovascular interventional surgery. It is known that local anesthetic infiltration or nerve blocks involved in the afferent trigeminal neuronal pathway may achieve prophylaxis of the peripheral TCR.[12] Therefore, based on the knowledge that a local intravenous injection of lidocaine can effectively prevent injection pain, we extrapolate it to the intra-arterial injection for cerebrovascular embolization surgery and anticipate blocking both activation of the trigeminal nerve and nerve–vascular communication.

In the present study, cardiac arrest suddenly occurred in three patients along with the onset of TCR. Normal circulation was resumed after discontinuing the surgical procedures, administration of atropine or epinephrine and even CPR. Asystole as a result of severe TCR occasionally occurs during Onyx embolization. Nevertheless, in the present study we found three cardiac arrests in 136 patients (2.2%) undergoing Onyx embolization. Such a rate of cardiac arrest might be due to the injection speed, viscosity and amount of DMSO/Onyx or enhanced vagal activity. In addition, the occurrence of TCR in four patients with HR dropping below 40 bpm and hypotension were corrected by 0.5 mg intravenous atropine. Notably, all the patients who experienced TCR were not pretreated with lidocaine injection, whereas the hemodynamics were relatively stable following prophylactic intra-arterial lidocaine injection. We therefore consider that a prophylactic intra-arterial injection of low-dose (5–20 mg) lidocaine is a novel strategy for the prevention and treatment of TCR during endovascular neurosurgery.

TCR is a well-described brainstem reflex which occurs during the stimulation of any branches of the trigeminal nerve.[19] When triggered by a meningeal vascular stimulus during DMSO/Onyx injection, the trigeminal nerve sends signals to the brainstem integrative centers including the sensory nucleus of the trigeminal nerve, the short internuncial nerve fibers in the reticular formation, and the efferent pathway in the motor nucleus of the vagus nerve and nucleus ambiguus. The fibers of the vagus or sympathetic nerves end in the myocardium, leading to autonomic changes (see online supplemental figure 2).

It has been reported that TCR may be accompanied by a decrease or increase in blood pressure.[20] There are two major subtypes of peripheral or central TCR. Peripheral stimulation of the trigeminal nerve co-activates the vagal and sympathetic nerves resulting in both hypertension (peripheral vasoconstriction) and bradycardia.[9] By contrast, central stimulation causes hypotension and bradycardia by generating profound activation of the cardiac vagal branch and distinct inhibition of the inferior cardiac sympathetic nerve.[10 14] In the present study we found that seven patients with TCR had a decrease in blood pressure which, in six patients, was >20%. Conversely, five patients had a decrease in HR but an increase in blood pressure. We noticed that patients who first experienced severe bradycardia were often followed by hypotension, whereas patients who first experienced hypertension had relatively mild bradycardia. These results suggest that central stimulation caused by endovascular embolization might potentially induce overactivation of the vagus nerve (bradycardia) and the extent of vagus nerve activation might determine the change in blood pressure. Severe bradycardia causes hypotension, as seen in the central type of TCR when the vagus nerve is profoundly activated, while relatively mild activation of the vagus nerve leads to hypertension due to simultaneous stimulation of the inferior cardiovascular sympathetic nerve (seen in peripheral TCR). In the lidocaine group, no patient had a decrease in HR or blood pressure while 10 patients had an increase in blood pressure of >20% during DMSO/Onyx injection. We therefore propose that the dosage of lidocaine used in this study could inhibit overactivation of the vagus nerve but have no effect on activation of the sympathetic nerve.

Lidocaine is a local anesthetic that can be used locally or regionally to produce a temporary loss of sensory, motor, and autonomic function. It binds to sodium channels within the neurocellular membranes, which temporarily blocks sodium influx into the cell preventing membrane depolarization.[21] Although all cellular membranes are affected, sensory nerve fibers are usually affected first because they are much thinner and can be easily penetrated,[22] thus intra-arterial injection of lidocaine might work as endovascular anesthesia. Lidocaine has an excellent safety profile when limited to a dose of <4.5 mg/kg, depending on the site of injection and rate of absorption.[23] In our study, injection of only 20 mg lidocaine through the arterial indwelling catheter into the cerebral vessels completely prevented TCR without any obvious adverse effects. Such a dose of lidocaine applied in the intracranial artery did not cause

Table 3 Outcome analyses and adverse events

Composite adverse events	Control group (n=68)	Lidocaine group (n=68)	P value
Patients, n (%)	29 (42.6)	13 (19.1)	0.003
TCR	12 (17.6)	0	<0.001
Heart arrest	3 (4.4)	0	0.24
Headache/dizziness	14 (20.6)	10 (14.7)	0.37
PONV	5 (7.4)	2 (2.9)	0.44
Muscle weakness	1 (1.5)	2 (2.9)	1.00
Aphasia	1 (1.5)	0	1.00
Hypopsia	2 (2.9)	1 (1.5)	1.00
Cerebral infarction	1 (1.5)	0	1.00

The components of the composite adverse events (intraoperative and within the first 24 hours after surgery) were TCR, heart arrest, dizziness, PONV, muscle weakness and other events (aphasia, hypopsia and cerebral infarction).
PONV, postoperative nausea and vomiting; TCR, trigeminocardiac reflex.

obvious central nerve system and cardiovascular toxicity under general anesthesia. Importantly, the potential risks of lidocaine on white matter dysfunction including behavioral and cognitive deficits were not observed, while motor problems (muscle weakness) rarely occurred. These observations confirm the safety and efficacy of 20 mg lidocaine in intracranial vessels.

DAVFs are abnormal connections between dural arteries and venous sinuses. The dura mater is innervated in part by branches of the trigeminal nerve and receives its vascular supply from the meningeal artery as well as meningeal branches of the occipital artery.[24] These vessels are mostly involved in the blood supply to the sensory area of the trigeminal nerve. Therefore, when the meningeal artery receives mechanical or chemical stimulation, the trigeminal nerve attached to the artery vessel is then activated leading to TCR. To some extent, these results support the anatomically specific triggering of TCR. In this study we found that patients with DAVF accounted for 75% of TCR episodes and the middle meningeal artery played a major role as one of the supplying vessels to the lesion site for the occurrence of TCR. We therefore believe that DAVF and embolization via the middle meningeal artery are risk factors for TCR during DMSO/Onyx injection.

CONCLUSION

In the present study, prophylactic intra-arterial injection of small doses of lidocaine through the indwelling catheter safely and effectively inhibited the trigeminal nerve cardiac reflex during cerebral vascular embolization. This new approach could be recommended for use during surgical procedures where there is a risk of TCR activation, especially in the case of recurrent and profound bradycardia in DAVF and embolization via the middle meningeal artery and its branches. As the communication between neurons and blood vessels is well known, such a strategy could be extended to use in all kinds of vascular interventional surgery to prevent and treat surgical manipulation-related neurovascular complications including pain and neuronal-vascular-cardiac reflex.

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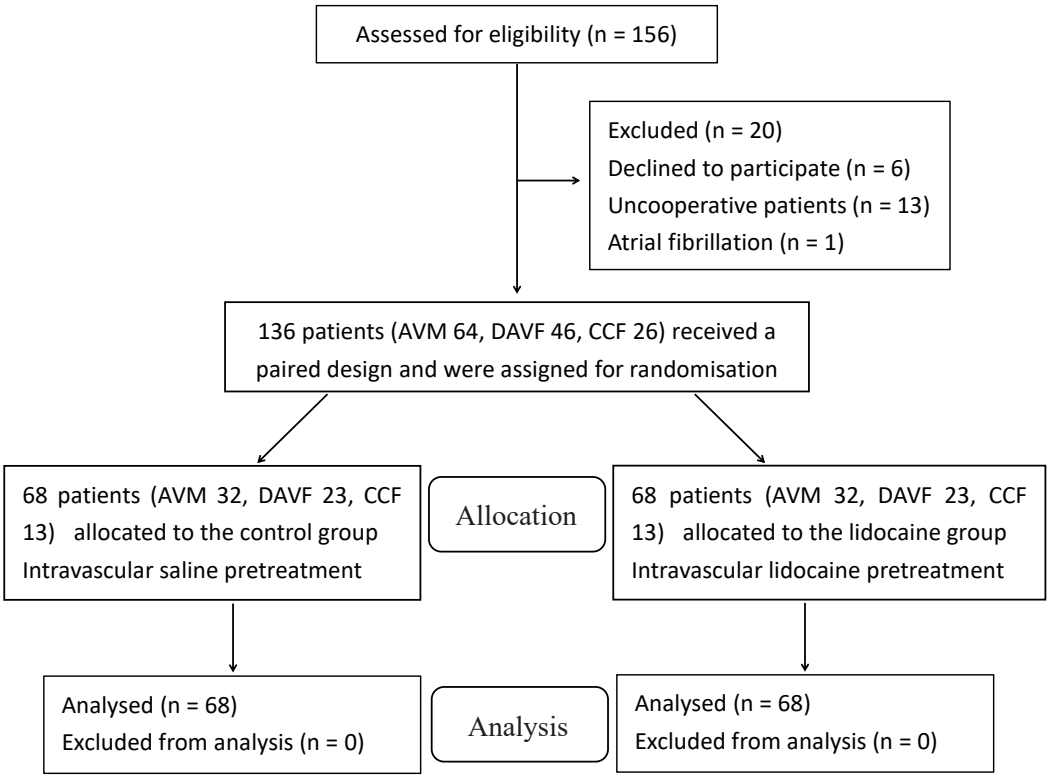


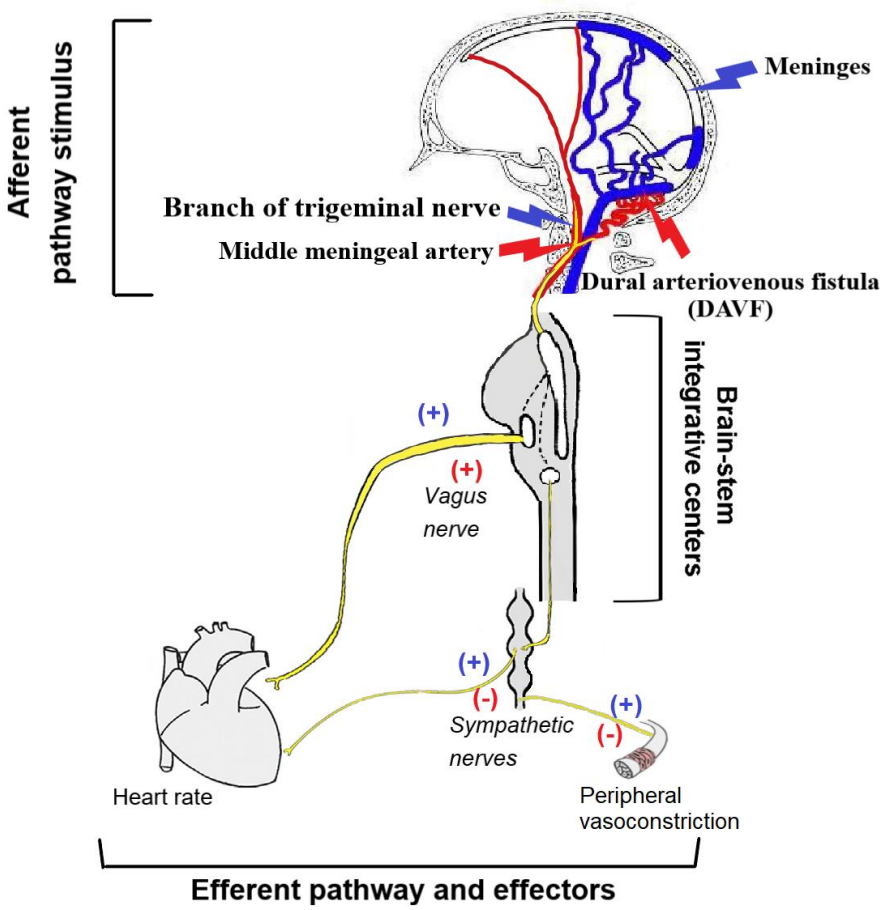
Supplementary Figure 1. Flow of participants through the study.

Supplementary Table 1. Description of the 12 cases who suffered TCR during embolization

Cases	Diagnosis	Comorbidity	Vessel of Embolization	HR	MAP	Treatment Approach	TCR Type
Case 1	DAVF	None	Middle meningeal artery	0	0	CPR	IV a
Case 2	CCF	Bradycardia	Cavernous sinus	0	0	Atropine	IV a
Case 3	DAVF	Hypertension	Middle meningeal artery	0	0	Atropine, CPR, Epinephrine	IV a
Case 4	DAVF	Diabetes	Middle meningeal artery	33	55	Atropine	IV a
Case 5	DAVF	None	Middle meningeal artery	31	51	Atropine	IV a
Case 6	DAVF	None	Middle meningeal artery	36	62	Atropine	IV a
Case 7	CCF	Bradycardia	Cavernous sinus	38	67	Atropine	IV a
Case 8	DAVF	None	Middle meningeal artery	42	105	N/A	IV b
Case 9	CCF	Hypertension	Cavernous sinus	41	121	N/A	IV b
Case 10	DAVF	None	Occipital artery	42	110	N/A	IV b
Case 11	DAVF	None	Vertebral artery branch	45	103	N/A	IV b
Case 12	DAVF	Hypertension, Diabetes	Middle meningeal artery	46	122	N/A	IV b

HR was the slowest with MAP recoded accordingly when TCR occurred during intra-arterial embolization. TCR type was defined according to the new classification scheme according to the onset of HR reduction [17]: IVa is defined when HR reduction appears early than MAP alteration and IVb type is classified if HR reduction follows MAP alteration.

N/A, not applicable.



Supplementary Figure 2. Schematic illustration of the autonomic neural pathway and effector activated as a consequence of trigeminal nerve stimulation trigged by meningeal vascular stimulus during DMSO/Onyx injection.

Endovascular embolization induced TCR is that signals triggered by central stimulation are sent to brainstem integrative centers including the sensory nucleus of the trigeminal nerve, the short internuncial nerve fibers in the reticular formation, and the efferent pathway in the motor nucleus of the vagus nerve and nucleus ambiguus. The fibers of the vagus or sympathetic nerves end in the myocardium and peripheral blood vessels, leading to autonomic changes that usually manifest as a negative chronotropy, or occasionally bradycardia with increased blood pressure. Patients with DAVF and the middle meningeal artery as a major supplying vessel to the lesion site are more likely to experience TCR with bradycardia and hypotension or hypertension.

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Date: 3/24/2022

Your Name: Zhaochu Sun

Manuscript Title: Prophylactic intra-arterial injection of lidocaine: a novel strategy to prevent endovascular embolization-induced trigeminocardiac reflex

Manuscript Number (if known): neurintsurg-2022-018735

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Date: 3/24/2022

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Your Name: Youli Hu

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