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ORIGINAL COMMUNICATION

Characteristics and relative factors of headache caused by cervicocerebral artery dissection

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Abstract

Objective To analyze the characteristics and relative factors of headache and neck pain due to cervicocerebral artery dissection (CAD).

Methods A total of 146 consecutive patients with CAD in Zhengzhou, China (2010–2017) were observed and registered prospectively. There were 60 (60/146) cases who complained of headache and neck pain, and we analyzed the characteristics of pain according to their clinical features. For the 130 (130/146) patients with complete clinical laboratory data, they were divided into two groups according to pain, and the relative factors of pain were analyzed.

Results The headache and neck pain in 60 CAD patients was mostly acute onset (98.3%), 70.6% (12/17) of patients with anterior circulation dissection and 88.4% (38/43) of patients with posterior circulation dissection complained of moderate to severe pain. 41.2% (7/17) of patients with anterior circulation dissection had temporal pain, while 46.5% (20/43) of the patients with posterior circulation dissection had occipital pain. There were 23.5% (4/17) and 32.6% (14/43) of patients with anterior and posterior circulation dissection complained of throbbing pain, respectively, 23.5% (4/17) and 20.9% (9/43) of patients with anterior and posterior circulation dissection complained of pulsating pain. The pain could occur in the ipsilateral (40.0%), bilateral (52.7%), or contralateral (7.3%) sites of the dissection. In the 130 patients, there were 56 cases (43.1%) in the pain group, and 74 cases (56.9%) in the non-pain group. Multivariate logistic regression analysis showed that female gender (OR 4.01, 95% CI 1.63–9.85, $P=0.002$), posterior circulation (OR 3.18, 95% CI 1.39–7.28, $P=0.006$), history of headache (OR 4.72, 95% CI 1.08–20.52, $P=0.039$), and low-density lipoprotein less than 1.8 mmol/L (OR 2.90, 95% CI 1.15–7.34, $P=0.025$) were risk factors of the occurrence of the pain related to CAD.

Conclusion The headache and neck pain caused by CAD is a moderate to severe pain occurring suddenly. The pain nature may be diverse but mostly like throbbing and pulsating. When the dissected artery is located in the posterior circulation, the pain is mostly in the occipital region, and mostly in the temporal region when the dissected artery is located in the anterior circulation. The pain can occur in ipsilateral, bilateral, or contralateral of the dissection. In addition, several factors might contribute to the occurrence of headache and neck pain.

Keywords Cervicocerebral artery dissection · Headache and neck pain · Pain features · Relative factors

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Introduction

Cervicocerebral artery dissection (CAD), which corresponds with a haematoma in the wall of a cervical or an intracranial artery is an acute cerebrovascular disease occurring at any age, but more common between 35 and 50 years old, and it may progress to an ischaemic event, such as ischemia and infarction of brain tissue [1–4]. Reports showed that in all ischemic stroke patients, CAD accounts for 2%, but up to 25% in people under 55 years [5]. Its clinical features include headache, neck pain, Horner's syndrome, cranial nerve palsy and cerebral ischemia [6]. In most cases, headache and neck pain may be the initial symptom before the ischemic stroke [7]. However, due to the fact that early features of CAD can mimic a painful musculoskeletal presentation, trigeminal neuralgia-like pain or migraine, the clinical diagnosis may be difficult when clear neurological features are not present [6, 8–10]. Our aim of this study was to analyze the characteristics and relative factors of headache and neck pain in CAD patients.

Materials and methods

Study population and case ascertainment

This study was based on consecutive single CAD cases examined from January 2010 to December 2017. A total of 146 patients in the Department of Interventional Neurology, First Affiliated Hospital of Zhengzhou University were observed and registered prospectively. All of them were diagnosed by experienced neurological physicians based on cranial imaging and clinical manifestations. Their clinical data was collected prospectively through face-to-face interviews. Patients gave informed consent before participating. The Ethics Committee of the First Affiliated Hospital of Zhengzhou University approved this study (Number: KW-2018-LW-006).

Digital subtraction angiography (DSA) was recognized as the gold standard for CAD, so all CAD patients underwent DSA with characteristic radiological signs, such as pearl-and-string sign, intimal flap, double lumen, and mural haematoma [11]. Magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) were also considered to be a necessary examination of cervicocerebral artery dissection. For patients with ischemic stroke, the infarction lesion should be located in the blood supply area of the involved artery. Patients with severe neck trauma, subarachnoid hemorrhage and cerebral hemorrhage were excluded.

For 146 patients, 60 (60/146) cases had headache and neck pain, and the characteristics of dissection-related pain in different parts were analyzed based on their clinical features. 130 (130/146) patients with complete clinical laboratory data were divided into two groups according to pain, and there were 56 (56/130) patients in the pain group and 74 (74/130) patients in the non-pain group, and the difference between the two groups were analyzed.

Data collected

For 60 CAD cases with headache and neck pain, we collected the data of age, gender, dissection site, ischemic stroke, and the initial clinical manifestations such as headache, dizziness, and focal neurological deficits. The pain's location, nature, intensity, frequency and initial symptoms were also collected by specialized neurologists through a routine neurological questionnaire face to face in the first days after hospital arrival. According to the visual analog scale (VAS), the intensity of the pain was classified as mild: VAS 1–3, moderate: VAS 4–6, severe: VAS 7–10.

For 130 cases with the complete laboratory data, we collected the data of age, gender, relative factors, and clinical laboratory results. The onset season was defined as spring, summer, autumn, winter. History of headache included migraine, tension-type headache and other forms of headache. Primary hypertension was defined by a history of antihypertensive treatment or blood pressure $\geq$ 140/90 mmHg during the non-acute phase. Diabetes mellitus was defined as a history of diabetes mellitus diagnosed by the treating physician with a fasting glucose > 7 mmol/L or use an antidiabetic therapy. With a boundary of 1.80 mmol/L which was the secondary prevention standards of ischemic cerebrovascular diseases, low-density lipoprotein (LDL) was divided into LDL < 1.80 mmol/L and LDL $\geq$ 1.80 mmol/L. History of smoking/drinking was divided into never smoking/drinking, past/current smoking/drinking. Previous infection: infection within 1 month before onset of artery dissection, including respiratory, digestive and other infections. Age, total cholesterol, triglycerides were compared using quantitative variables (Fig. 1).

Statistical analysis

With the help of Excel, the patient database was established. Quantitative variables were expressed as mean ± standard deviation, Qualitative variables were expressed in terms of frequency and percentage. Differences in two groups were examined by means of Student's *t* test, Chi square test or Fisher's exact test, when appropriate. The above-mentioned features with significant significance were forced into the multivariate logistic regression equation collectively. All

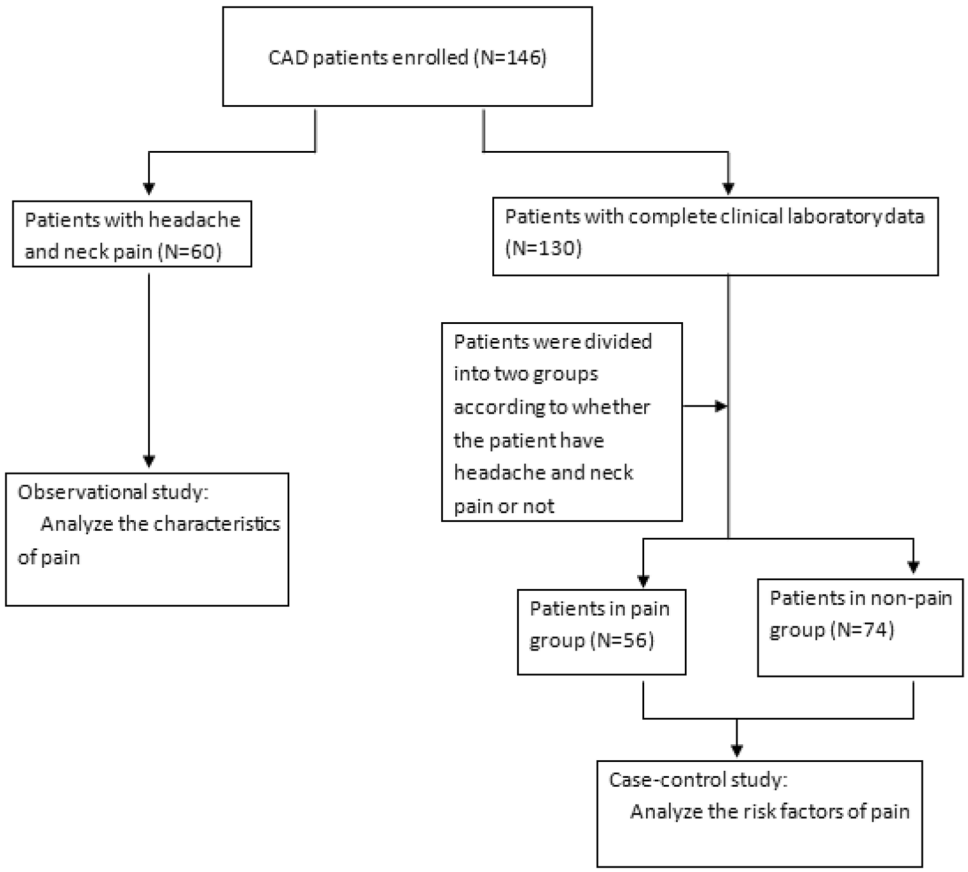

Fig. 1 Flowchart

data were analyzed using SPSS 22.0, and $P < 0.05$ was considered statistically significant.

Results

This study included a total of 146 patients, of whom 74.0% (108/146) cases were males, 26.0% (38/146) were females, and the average age was (50.9 ± 12.6) years. 70.5% (103/146) cases had ischemic stroke and 41.1% (60/146) cases had headache and neck pain.

The pain characteristics of 60 patients caused by CAD

Of the 60 CAD patients with headache and neck pain, 98.3% (59/60) patients had acute onset pain, and only one case increased gradually. There were 33.3% (20/60) patients with headache and neck pain as initial symptom, 6 of whom developed with ischemic events. For 17 (17/60) patients with anterior circulation dissection, there were 13 (76.5%) patients with neck carotid artery dissection, 4 (23.5%) patients with intracranial carotid artery and branches dissection. For 43 (43/60) patients with posterior circulation dissection, there were 5 (11.6%) patients with neck vertebral artery dissection, 38 (88.4%) patients with intracranial vertebral and basilar artery and branches dissection. The difference in sites of the dissection was statistically significant ($P < 0.001$). Of the 43 cases with posterior circulation dissection, 33 cases had intracranial (V4) segment dissection.

For the localizations of dissection-related pain, 41.2% (7/17) of patients with anterior circulation dissection had the temporal pain, while 46.5% (20/43) of the patients with posterior circulation dissection had occipital pain. Except for 5 (5/60) cases with basilar artery dissection, pain could be located on the ipsilateral side (40.0%), bilateral (52.7%), or contralateral (7.3%) of the dissection; There were 23.5% (4/17) and 32.6% (14/43) of patients with anterior and posterior circulation dissection complained of throbbing pain, respectively. There were 23.5% (4/17) and 20.9% (9/43) of patients with anterior and posterior circulation dissection complained of pulsating pain, respectively. There were 70.6% (12/17) and 88.4% (38/43) of patients with anterior and posterior circulation dissection had moderate to severe pain, The frequency of pain could be continuous (47.1%) or intermittent (52.9%) for patients with anterior circulation dissection, and could be continuous (46.5%) or intermittent (53.5%) for patients with posterior circulation dissection. There were 17.6% (3/17) and 32.6% (14/43) patients with anterior and posterior

circulation accompanied by nausea and/or vomiting. The duration of the anterior circulation dissection-related pain ranged from 4 days to 3 months (median 15 days), except for 5 (5/43) patients who still had headache during the 6 months follow-up, and the duration of the posterior circulation dissection-related pain could be 5 days to 5 months (median 20 days) (Tables 1, 2, 3).

Analysis of pain relative factors in 130 CAD patients with complete clinical laboratory data

(1) 130 patients with complete clinical laboratory data were divided into two groups depending on whether the patient had headache and neck pain or not, and the relative factors of pain in CAD patients were analyzed. The results showed that there were significant

Table 1 Localizations of dissection-related pain according to the dissected artery (*n*, %)

Pain localization	Anterior circulation			Posterior circulation		
	NCAD (*n* = 13)	ICABD (*n* = 4)	Total (*n* = 17)	NVAD (*n* = 5)	IVBABD (*n* = 38)	Total (*n* = 43)
Frontal	1 (7.7)	0	1 (5.9)	0	0	0
Periorbital	1 (7.7)	0	1 (5.9)	0	0	0
Teeth/cheek/ear	0	0	0	0	4 (10.5)	4 (9.3)
Parietal	2 (15.4)	0	2 (11.8)	0	3 (7.9)	3 (7.0)
Temporal	5 (38.5)	2 (50.0)	7 (41.2)	3 (60.0)	5 (13.2)	8 (18.6)
Occipital	4 (30.8)	0	4 (23.5)	1 (20.0)	19 (50.0)	20 (46.5)
Neck	3 (23.1)	0	3 (17.6)	3 (60.0)	4 (10.5)	7 (16.3)
Whole head	1 (7.7)	2 (50.0)	3 (17.6)	0	2 (5.3)	2 (4.7)
Unilateral head	0	0	0	1 (20.0)	3 (7.9)	4 (9.3)
Moving pain	0	0	0	0	4 (10.5)	4 (9.3)

NCAD neck carotid artery dissection, *ICABD* intracranial carotid artery and branches dissection, *NVAD* neck vertebral artery dissection, *IVBABD* intracranial vertebral and basilar artery and branches dissection

Table 2 Nature of dissection-related pain according to the dissected artery (*n*, %)

Nature	Anterior circulation			Posterior circulation		
	NCAD (*n* = 13)	ICABD (*n* = 4)	Total (*n* = 17)	NVAD (*n* = 5)	IVBABD (*n* = 38)	Total (*n* = 43)
Throbbing	3 (23.1)	1 (25.0)	4(23.5)	2 (40.0)	12 (31.6)	14 (32.6)
Pulsating	3 (23.1)	1 (25.0)	4 (23.5)	0	9 (23.7)	9 (20.9)
Dull	1 (7.7)	1 (25.0)	2 (11.8)	0	8 (21.1)	8 (18.6)
Stabbing	2 (15.4)	0	2 (11.8)	2 (40.0)	2 (5.3)	4 (9.3)
Constrictive	2 (15.4)	1 (25.0)	3 (17.6)	0	3 (7.9)	3 (7.0)
Electrical	0	0	0	1 (20.0)	2 (5.3)	3 (7.0)
Not available	2 (15.4)	0	2 (11.8)	0	2 (5.3)	2 (4.7)

NCAD neck carotid artery dissection, *ICABD* intracranial carotid artery and branches dissection, *NVAD* neck vertebral artery dissection, *IVBABD* intracranial vertebral and basilar artery and branches dissection

Table 3 Intensity of dissection-related pain according to the dissected artery (*n*, %)

Intensity	Anterior circulation			Posterior circulation		
	NCAD (*n* = 13)	ICABD (*n* = 4)	Total (*n* = 17)	NVAD (*n* = 5)	IVBABD (*n* = 38)	Total (*n* = 43)
Mild	3 (23.1)	1 (25.0)	4 (23.5)	0	3 (7.9)	3 (7.0)
Moderate	3 (23.1)	3 (75.0)	6 (35.3)	3 (60.0)	11 (28.9)	14 (32.6)
Severe	6 (46.2)	0	6 (35.3)	2 (40.0)	22 (57.9)	24 (55.8)
Not avaliable	1 (7.7)	0	1 (5.9)	0	2 (5.3)	2 (4.7)

NCAD neck carotid artery dissection, *ICABD* intracranial carotid artery and branches dissection, *NVAD* neck vertebral artery dissection, *IVBABD* intracranial vertebral and basilar artery and branches dissection

differences between the two groups as follows: (1) Gender ($P=0.006$), the pain group had 22 (39.3%) females, and the non-pain group had 13 (17.6%) females. (2) Dissection sites ($P=0.002$), the pain group had 42 (75.0%) cases located in posterior circulation, and the non-pain group had 36 (48.7%) cases. (3) Drinking ($P=0.038$), the pain group had 13 (23.2%) cases with drinking history, and the non-pain group had 30 (40.54%) cases. (4) History of headache ($P=0.009$), the pain group had 10 (17.9%) cases with drinking history, and the non-pain group had 3 (4.1%) cases. (5) Previous infection ($P=0.009$), the pain group had 13 (23.2%) cases with previous infection, and the non-pain group had 5 (6.8%) cases. (6) Low-density lipoprotein (LDL) ($P=0.006$), the pain group had 21 (37.5%) cases with LDL < 1.8 mmol/L, and the non-pain group had 12 (16.2%) cases (Table 4).

(2) Multivariate logistic regression analysis.

The above-mentioned factors with significant difference were forced into the multivariate logistic regression equation collectively and the results showed that female gender (OR 4.01, 95% CI 1.63–9.85, $P=0.002$), posterior circulation (OR 3.18, 95% CI 1.39–7.28, $P=0.006$), history of headache (OR 4.72, 95% CI 1.08–20.52, $P=0.039$), and LDL less than 1.8 mmol/L (OR 2.90, 95% CI 1.15–7.34, $P=0.025$) were risk factors of the occurrence of the pain related to CAD (Table 5).

Table 5 Analysis of risk factors of pain in patients with CAD

Clinical data	OR	OR (95% CI)	*P* value
Gender	4.01	1.63–9.85	0.002
Location	3.18	1.39–7.28	0.006
History of headache	4.72	1.08–20.52	0.039
LDL	2.90	1.15–7.34	0.025

CI confidence interval, *LDL* low-density lipoprotein

Discussion

In the cerebral infarction patients, patients with dissection were younger compared with those without dissection, and the clinical features were broad, such as headache, ischemic or hemorrhagic stroke [11, 12]. With the development of imaging techniques in recent years, CAD without neurological deficits have been reported frequently [13]. It is reported that headache and neck pain caused by CAD is often acute onset, unexplained or different from previous episodes [14, 15] and can be the only warning symptom preceding the focal neurological deficit. In this study, approximately 13.7% of patients with CAD only presented with pain as the initial symptom, which was consistent with the reports of Maruyama et al. (15.7%) [16], but lower than the results of Yamada et al. (31.7%) [17], who performed head MRI as the first test for patients, even though the patient only presented with a sudden headache or dizziness within a few hours. According to the literature, intracranial dissections tend to occur in the

Table 4 Comparison of clinical data in both groups

	With pain ($n=56$)	Without pain ($n=74$)	Total ($n=130$)	*P* value
Gender (female) (*n*, %)	22 (39.3)	13 (17.6)	35 (26.9)	0.006
Age (mean ± SD) year	49.3 ± 13.3	52.1 ± 12.5	50.9 ± 12.9	0.22
Posterior circulation (*n*, %)	42 (75.0)	36 (48.6)	78 (60.0)	0.002
Ischaemic event (*n*, %)	36 (64.3)	55 (74.3)	91 (70.0)	0.22
Spring (*n*, %)	13 (23.2)	17 (23.0)	30 (23.1)	0.97
Summer (*n*, %)	14 (25.0)	22 (29.7)	36 (27.7)	0.55
Autumn (*n*, %)	11 (19.6)	17 (23.0)	28 (21.5)	0.65
Winter (*n*, %)	17 (30.4)	18 (24.3)	35 (26.9)	0.44
Smoking (*n*, %)	21 (37.5)	34 (45.9)	55 (42.3)	0.33
Drinking (*n*, %)	13 (23.2)	30 (40.5)	43 (33.1)	0.038
History of diabetes (*n*, %)	5 (8.9)	10 (13.5)	15 (11.5)	0.42
History of hypertension (*n*, %)	27 (48.2)	46 (62.2)	73 (56.2)	0.11
History of headache (*n*, %)	10 (17.9)	3 (4.1)	13 (10.0)	0.009
Previous infection (*n*, %)	13 (23.2)	5 (6.8)	18 (13.8)	0.007
LDL < 1.8 mmol/L (*n*, %)	21 (37.5)	12 (16.2)	33 (25.4)	0.006
Total cholesterol (mean ± SD) mmol/L	3.89 ± 1.07	3.94 ± 1.05	3.92 ± 1.06	0.76
Triglycerides (mean ± SD) mmol/L	1.31 ± 0.70	1.25 ± 0.53	1.28 ± 0.61	0.60

SD standard deviation, *LDL* low-density lipoprotein

posterior circulation more commonly, while the opposite is true for extracranial dissections [18, 19], and the intracranial segment (V4) of the vertebral artery was vulnerable to dissection [20]. This study displayed that the posterior circulation was more prone to pain than the anterior circulation, and the intracranial segment (V4) of the vertebral artery was more prone to headache and neck pain.

The pain caused by CAD can occur in any part of the head and neck either alone or in combination. Even if the dissection is unilateral, headache can be bilateral or diffuse [16, 21, 22]. In this study, pain can occur in the ipsilateral (40.0%), bilateral (52.7%), or contralateral (7.3%) sites of the dissection. Mokri et al. found that the pain caused by CAD was related to the nerves around the blood vessels [22]. Therefore, the pain site was usually associated with the location of the dissection [18]. In the vertebral artery dissection, pain in neck and occipital is common, while in the internal carotid artery, the temporal and facial pain is more frequent than the neck pain. But the pain is not always located in the typical pain area. For example, some patients with vertebral artery dissection present with pain in the orbital part, and others with internal carotid artery may be suffering from occipital pain [8, 17, 23–25]. In this study, 41.2% of patients had the temporal pain when the dissection was in anterior circulation, and 46.5% of the patients had occipital pain when the dissection was in posterior circulation. For most CAD patients, the pain is acute onset and moderate to severe, which is different from any previously experienced pain and often requires analgesics [15, 22, 26]. Similarly, 70.6% and 88.4% patients with anterior and posterior circulation dissection complained of moderate to severe pain in this study. In addition, the literature reported that the nature of the pain could be like throbbing and pulsating similar to migraine, dull and constrictive [16, 21, 27] similar to tension-type headache, stabbing and electrical similar to neuropathic pain [28, 29]. In this study, 47.0% and 53.5% patients complained of migraine-like pain in anterior and posterior circulation dissection, respectively. The frequency of pain attack could be continuous or intermittent. The duration of the dissection-related pain could last for some days, for several weeks, sometimes even for several months.

Dissection refers to a tear in the wall of an artery, the pathological specimens of CAD patients usually appeared the destruction of the internal elastic layer [30, 31]. The blood clot's direct pressure on the vessel wall and the distention of the vessel stimulating the sensory nerve fibers around it may be the direct reason of pain [32–35]. The nerve terminals can also release proinflammatory neurotransmitters that cause pain away from the actual site of the dissection [18]. Another possible mechanism of pain is cortical spreading depression (CSD), which is related with the spreading waves of intense neuroglial depolarizations with the changes in cerebral blood flow [36]. And, the pain could be present by triggering the trigeminovascular system [21]. This study displayed that the posterior circulation was more prone to pain than the anterior circulation, which may be associated with a more intensive vasculature in the posterior circulation system [37], and the posterior circulation artery might contribute to increase susceptibility to spreading depolarizations [38, 39]. LDL is well-known as a risk factor of atherosclerosis, and this study found that CAD patients with LDL less than 1.8 mmol/L tended to have pain. We speculated that these patients had relatively mild atherosclerosis and good vascular elasticity so as to result in headaches by stimulating the trigeminovascular system [40–42]. It is reported that women and patients with a history of headache are more likely to develop headache in ischemic stroke patients [38]. The same conclusion was reached in the exploration of relative factors for CAD patients showing pain.

This study has several limitations. First, a number of cases do not have complete headache characteristic information. Second, patients with imaging-negative subarachnoid hemorrhage could not be excluded. Although these limitations, our study also has several strengths. Our study is exhaustive, continuous and has a prospective registry of CAD patients, and with clinically meaningful outcome measures.

Conclusion

In summary, cervicocerebral artery dissection should be suspected when patients complain of unexplained, moderate to severe pain occurring acute. And the posterior circulation is more prone to pain than the anterior circulation. The pain can be continuous or intermittent, and its nature may be diverse but mostly like throbbing and pulsating. When the dissected artery is located in the posterior circulation, the pain is mostly in the occipital, and mostly in the temporal region when the dissected artery is located in the anterior circulation. The pain can occur in ipsilateral, bilateral, or contralateral of the dissection. Female gender, posterior circulation dissection, LDL levels less than 1.8 mmol/L and a history of headache were risk factors of headache and neck pain due to CAD.

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Compliance with ethical standards

Conflicts of interest The authors declare that there is no conflict of interest.

Ethical approval The Ethics Committee of the First Affiliated Hospital of Zhengzhou University approved this study (Number: KW-2018-LW-006).

Informed consent All subjects gave their informed consent prior to their inclusion in the study.

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