

**REVIEW**

# Cardiac cephalalgia

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**Competing interests:**

The authors have declared that no competing interests exist

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**Summary**

Cardiac cephalalgia has a small incidence, but unrecognized it can prolong the time to diagnose a life-threatening condition such as acute coronary event. According to its clinical presentation, it can refer to a migraine. Even in the absence of clinically and laboratory evident signs, the diagnosis of cardiac migraine should be kept in mind because sometimes it is the only symptom of a threatening coronary event. The choice of treatment depends on a correctly established diagnosis. A reckless inclusion of vasoconstrictors as a standard therapeutic modality of migraine in a patient with a cardiac cephalalgia could worsen ischemia and endanger the patient's life. By solving an acute coronary event conservatively, with percutaneous coronary interventions or coronary "bypass," cardiac cephalalgia is eliminated as well.

**Keywords:** Migraine, cardiac cephalalgia, ischemia, coronary

## INTRODUCTION

Headaches belong to the most common diseases affecting the human species. In 2016, it was estimated that almost 3 billion people suffered from some form of a headache (1). Headaches are divided into primary and secondary headaches according to their cause. Cardiac cephalalgia belongs to the group of secondary (symptomatic) headaches.

Cardiac cephalalgia ("heart headache or anginal headache") was first described by Lipton et al. in 1997 as a secondary headache phenomenon that occurred in conditions of cardiac ischemia (2). It is defined as a headache whose characteristics are similar to those of a migraine, which is usually, but not always, initiated by exertion, which occurs during an episode of myocardial ischemia, and which is relieved by nitroglycerin therapy (3). The choice of therapeutic measures in treating this condition must be carefully made because using vasoconstrictors (e.g., triptans), and specific antimigraine drugs, could worsen myocardial ischemia and be fatal.

## EPIDEMIOLOGY

The frequency of cardiovascular diseases and ischemic heart disease, as comorbidities, in patients with primary headaches is higher than in general population (7% vs. 2.6%) (4). In contrast, a headache can sometimes be a predictor of cardiovascular disease or the first clinical presentation of angina pectoris and acute myocardial ischemia. In ischemic heart disease, the most common localization of angina is in the middle of the chest, with propagation to the arm, back, neck, jaw, or epigastrium. The occurrence of a headache as the main or the only symptom of ischemic heart disease is infrequent. Based on previous data from literature, in 5.2%-6% of patients, a headache is an accompanying symptom of acute myocardial ischemia. In only 3.5%, the head was the only place of pain (5-6) during the coronary event, although the headache was not the only symptom of the disease (6). Despite the current data on the prevalence of cardiac cephalalgia, its characteristics and pathophysiology are still insufficiently known.

## PATHOPHYSIOLOGY OF CARDIAC CEPHALALGIA

Four hypotheses could explain the mechanism of its origin (7-9).

According to the first hypothesis, pain with predominance of a headache is transmitted in 50% to 60% of patients by sympathetic fibers, in 10% to 20% of patients by parasympathetic fibers, and through both types of fibers in 30% to 40% of patients. This phenomenon could be due to the convergence of afferent autonomic visceral fi-

bers, which carry nociceptive stimuli from the heart via dorsal roots from C8 to TH5, and somatic sensory fibers, which innervate the chest and the arms, on typical neurons of the posterior horns of the spinal cord, sympathetic ganglions, or thalamus. The pain manifested in the lower jaw is a consequence of the convergence of autonomic fibers and trigeminal somatic fibers in the nucleus of the trigeminus. In occipital headaches, the convergence of fibers occurs in the typical neurons of the posterior horns in the upper part of the cervical spinal cord. Parasympathetic sensory impulses traveling via the vagus converge with somatic sensory impulses in the thalamus. Based on this convergence theory, afferent somatic and visceral fibers converge on the same neurons. When visceral afferent impulses stimulate neurons, information in the higher centers of the central nervous system is transmitted to the corresponding somatic regions (2, 10-11). The concentration of cardiac afferent autonomic fibers varies for each part of the heart. A large concentration of sympathetic fibers is thought to be located in the anterior part of the left ventricle.

In contrast, parasympathetic fibers are concentrated and innervate the inferior and posterior walls of the left ventricle. Since perfusion of the anterior wall of the left ventricle is achieved through the anterior left descending artery, and the posterior and lower walls of the ventricle are perfused through the right coronary and circumflex arteries, the dominant activation of the fibers depends on the artery responsible for myocardial ischemia. Therefore the localization of cardiac cephalalgia depends on the part of the heart affected by ischemia (12-13).

The second hypothesis is based on a sudden reduction in cardiac output during ischemia. Consequently, pressure increases in the left ventricle and then in the right atrium as well, and there is a decrease in the venous drainage of blood from the head and an increase in intracranial pressure (2). Due to the distension of the head and neck blood vessels, the nociceptive stimulation of intracranial structures (blood vessels, brain cells) increases.


According to the third hypothesis, pain is caused by the release of neurochemical mediators due to tissue ischemia. Mediators such as serotonin, bradykinin, histamine, substance P, and atrial natriuretic peptide have a solid vasodilatory effect on the arteries in the brain (2,11).

The fourth theory assumes that the headache could be present due to the simultaneous presence of vasospasm on the coronary and small intracranial arteries due to sympathetic activation by myocardial ischemia (14-16).

## CLASSIFICATION OF CARDIAC CEPHALALGIA

Cardiac cephalalgia was introduced in the second edition of the International Classification of Headache Disorders (ICHD-2) as a secondary headache related to homeostasis disorders (3). As soon as 2004, based on a review of

**Table 1.** ICHD-3 diagnostic criteria for cardiac cephalgia

10.6 Cardiac cephalgia
A. Any headache that meets criterion C
B. Confirmed acute myocardial ischemia
C. Evidence of cause confirmed by at least two of the following:
1. The headache developed in close relation with the onset of acute myocardial ischemia
2. One or both of the following:
a. Headache significantly worsened concurrently with worsening ischemia
b. The headache significantly eased or disappeared at the same time as ischemia receded
3. A headache has at least two of the four characteristics:
a. Moderate to severe intensity
b. Accompanied by nausea
c. Isn't accompanied by photophobia or phonophobia
d. Worsens with exertion
4. Headache resolves with nitroglycerin use
D. Not better explained by another ICHD-3 diagnosis


literature, the criteria were revised. According to the criteria from the latest classification, ICHD-3, cardiac cephalgia is described as a migraine-like condition that is usually (but not always) triggered by exertion and occurs during an episode of myocardial ischemia (3). **Table 1.** shows the most recent criteria for this type of headache.

## CLINICAL PRESENTATION

Risk factors for cardiovascular disease such as advanced age, hypertension, hyperlipidemia, diabetes, smoking, and positive family history of vascular disease are commonly present in patients with cardiac cephalgia. Many patients with cardiac cephalgia may not have these risk factors (17).

Cardiac cephalgia can vary considerably in its clinical presentation. It often resembles other forms of primary or secondary headaches in terms of their characteristics and triggering factors (e.g., exertion). The presentation of the disease can vary by location, time, primary symptoms, and the presence of risk factors for a cardiac event.

Concerning localization, it can be bifrontal, bitemporal, or occipital. Depending on the onset, it can be acute, subacute, or intermittent. The nature of the pain ranges from pulsations, stabbing pain, throbbing pain, dull pain, shooting pain, or explosion-like pain. Headaches of this type can also be associated with signs from the autonomic nervous system: nausea, vomiting, redness or paleness of the face/skin, and sweating. The duration of the headache can vary from a few minutes to several hours, and its severity can range from moderate to severe. Mostly, the majority of hospitalized patients registered a severe form of headache.

With myocardial ischemia, a headache may or may not be accompanied by chest pain. In most cases, patients

also had chest pain (17-18), but cases of patients whose headache was the only symptom of angina pectoris or a coronary event have also been described (19-21).

## DIAGNOSIS

A headache with accompanying symptoms of myocardial ischemia is a typical manifestation of cardiac cephalgia. In addition to a positive medical history and data on previous headaches and accompanying ischemia, an electrocardiogram (ECG) should be performed at rest and during exertion, and cardiac enzymes: Creatinine Phosphokinase - Muscle/Brain (CPK-MB), myoglobin and troponin may be helpful.

The problem in establishing the correct diagnosis is usually the absence of typical chest pain. However, a common cardiac cephalgia that worsens with exertion and resolves with administered nitroglycerin should raise suspicion about this diagnosis. Not all forms of cardiac cephalgia worsen at exertion, so other factors, including new or unusual headaches, age over 50 years, and vascular risk factors: current or previous smoking, hypertension, hyperlipidemia, diabetes, and positive family history, should be considered. The presence of any of the above-mentioned factors requires an urgent neurological examination that includes additional diagnostics in the form of magnetic resonance imaging, imaging of cerebral arteries, EKG, nitroglycerin test, and consultation with a cardiologist. Lumbar puncture and cerebrospinal fluid (CSF) analysis could help rule out subarachnoid hemorrhage or meningitis/encephalitis as the most common differential diagnoses. Continuous monitoring of cardiac function, exercise tolerance test, and dobutamine stress echocardiography could be considered with a cardiologist in order to determine the changes that occur during an episode of cardiac cephalgia (22).

In patients in whom all findings, including ECG, laboratory tests, neurological findings, neuroimaging, and findings of CSF and electroencephalogram, are negative, the resolution of ST depression can be determined by a stress test (18). Sometimes, in order to establish a diagnosis, it is necessary to suspect cardiac cephalgia, even when there are no other symptoms or signs of angina pectoris or myocardial infarction in addition to the headache. Coronary angiography was an essential diagnostic tool when the ECG and stress test did not show signs of myocardial ischemia.

In a review of previous literature, which included 59 patients with cardiac cephalgia, the majority of patients were men (62.7%), middle-aged or older (over 50 years, 79.7%). In the most significant number of cases, pain occurred during some kind of effort, while in 27.1%, it occurred at rest. In 39% of patients, pain affected the occipital region, mainly on both sides. On the ECG, 39% of patients had ST elevation, and 15.2% had ST depression.

In 25% of patients whose cardiac enzymes were measured in the laboratory, an increase in enzymes was present in 21%. The underlying clinical condition in 50.8% of patients was acute myocardial infarction, in 47.5% it was angina, and in 1.7% it was cardiomyopathy. Coronary occlusion or severe stenosis were present in almost all patients with (8).

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cardiac cephalgia includes a wide range of diagnoses. It includes primary headache syndromes, such as migraine and tension headaches, and secondary headache syndromes, especially those related to effort.

Due to the high risk for the patient, it is essential to rule out the existence of subarachnoid hemorrhage (SAH), which is clinically manifested by the occurrence of a “thunderbolt-thunderclap” headache that may resemble the occipital localization of cardiac cephalgia. Pain may be the only symptom of SAH. The intensity of this headache is disabling and unbearable. The diagnosis is based on brain computerized tomography (CT) of the brain and lumbar puncture that proves the presence of blood in the cerebrospinal fluid when a further urgent care by a neurosurgeon is necessary.

Establishing a diagnosis is much more difficult if a headache appears to be the only symptom of ischemia. In such situations, suspicion of acute myocardial ischemia is established based on data on the patient’s age. Older age is highly indicative of a secondary origin of headaches.

Data on risk factors for vascular diseases as well as the occurrence of headaches in conditions of stress and exertion, additionally help in establishing the diagnosis. In the case of new-onset headaches in patients over 50, it is recommended to perform an ECG and check cardiac enzymes.

It is essential to differentiate between cardiogenic headaches and the occurrence of migraine headaches. Migraine headaches usually appear between the second and third decade of life, more often in women, and the first headaches can also appear during the first menstrual cycle. Migraine headaches can also be accompanied by mood swings, tremors, and increased appetite. The intensity of the headache, which usually starts in the morning, increases and reaches its maximum during the day. Both types of headaches may be accompanied by signs of the autonomic nervous system in the form of nausea and may worsen at exertion but also at rest. The correct diagnosis affects the choice of therapy. Vasoconstrictor drugs used in migraine therapy (triptans or ergotamine derivatives) are contraindicated in cardiac cephalgia. Although these drugs exert their primary effect (antag-

onists of 5-HT<sub>1B-1D</sub> receptors) on meningeal arteries, perivascular sheaths of trigeminal endings, and the central nervous system, their minimal vasoconstrictive effect was also observed on coronary vessels (23-24).

When there are no other symptoms of ischemia, the differential diagnosis should be thought of as headaches related to effort, and primary headache associated with sexual activity and cough headache. The common feature of these headaches is the sudden onset of pain strictly related to a specific effort. The pain is usually bilateral, of high intensity, pulsating, and can last from a few minutes to 24 hours. These headaches must rule out secondary causes with appropriate diagnostic procedures.

A headache can also occur after the administration of nitroglycerin, usually in the form of a migraine attack due to the vasodilator effect of nitrates. The pain develops within 10 minutes of drug administration, being primarily bilateral, with stabbing worsened at exertion, and it resolves one hour after drug administration. Late forms of this headache may occur in people who are otherwise prone to headaches. They also occur after nitro preparations but disappear after 72 hours (3). In the differential diagnosis of these patients, it is crucial to assess the time of drug administration and the time when symptoms appear.

Extra cephalic presentations of migraine headaches should also be suspected in the differential diagnosis. They appear in uncontrolled pain syndromes, including migraines (25). Extra cephalic manifestations of migraine have been described in literature, but chest pain in the form of allodynia as part of migraine is rare. In a study involving 33 patients, Roland showed that chest pain occurred immediately after a migraine. Visual analog scale (VAS) median headache intensity was 8/10, and the most common localization was the left hemicrania. The median duration of migraine was about 26 hours. The majority, about 76% of patients, described chest discomfort as pain. The median VAS of chest pain was 7/10. Chest pain did not change at exertion, but it increased at palpation (26).

Chest pain and headache can occur as part of many other conditions. According to the Anxiety and Depression Association of America (ADAA), chest pain and headaches can occur with panic attacks as part of anxiety. In a panic attack, chest pain resembles angina pain and is usually accompanied by other signs such as tachycardia, shortness of breath, weakness, sweating, and tremors. In autoimmune diseases such as systemic lupus, other organs and tissues, such as the heart and blood vessels, are affected. Therefore, these patients may have symptoms of chest pain and headache that resemble cardiogenic shock. As a part of other diseases and conditions such as fibromyalgia, carbon monoxide poisoning, sarcoidosis, peptic ulcer, pneumonia, and tuberculosis, a similar clinical presentation of headache may occur, which has cardiogenic characteristics and can be accompanied by chest pain.



## MANAGEMENT OF PATIENTS WITH CARDIAC CEPHALALGIA

Very often, this form of headache is misdiagnosed as a migraine. According to data from literature, these patients can have undiagnosed cardiac cephalgia for years before acute myocardial infarction occurs (19). Triptans should be avoided in patients with myocardial infarction, cerebrovascular insult, uncontrolled hypertension, or diabetes. Tricyclic antidepressants, selective serotonin reuptake inhibitors, and selective serotonin-norepinephrine reuptake inhibitors can increase blood pressure and should be used with caution. Nitroglycerin causes vasodilation and worsens migraine, and with its use, headaches can be expected in patients who commonly suffer from migraine headaches.

In carrying out the necessary therapy, the cooperation of neurologists and cardiologists is essential. In addition to the standard therapy for patients with a coronary event, nitro-derivatives relieve symptoms. However, performing recanalization of the affected coronary artery or arteries is of crucial importance for these patients. In line with that, percutaneous coronary intervention or coronary bypass is crucial in solving headaches. With a successful intervention, myocardial ischemia is resolved, and pain symptoms subside. A recurrent headache may indicate coronary artery restenosis (27-28).

## CONCLUSION

The present review summarizes the current knowledge on cardiac cephalgia and emphasizes the importance of recognizing headaches as a symptom of certain, sometimes very serious and life threatening, conditions. Headaches as a part of the clinical presentation of cardiovascular disorders are not unusual, but their occurrence as the only symptom of cardiovascular events is rare. Keeping cardiac cephalgia diagnosis in mind, even without laboratory and clinically evident signs, is necessary because it can be the only manifestation of serious ischemic events. It is essential to differentiate cardiac cephalgia from migraine because introducing vasoconstriction drugs, as a standard therapeutic modality for migraine, can be life-threatening in the setting of a coronary event.

## Conflict of interests:

The authors have declared that there are no competing interests.

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## KARDIOGENA GLAVOBOLJA

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### Sažetak

Kardiogena glavobolja je retka po svojoj učestalosti, ali neprepoznata može da produži vreme dijagnostikovanja životno ugrožavajućeg stanja kao što je akutni koronarni događaj. Po svojoj kliničkoj prezentaciji može upućivati na migrensku glavobolju. Čak i u odsustvu klinički i laboratorijski evidentnih znakova, dijagnozu kardiogene migrene bi trebalo imati na umu jer je nekada ona jedini simptom pretećeg koronarnog događaja. Izbor lečenja

zavisí od pravilno postavljene dijagnoze, a nesmotreno uključivanje vazokonstriktora kao standardnog terapijskog modaliteta migrene, kod pacijenta sa kardiogenom glavoboljom bi moglo pogoršati ishemijsku i životno ugroziti pacijenta. Rešavanjem akutnog koronarnog događaja konzervativnim putem, perkutanom koronarnom intervencijama ili koronarnim "by-pass"-om otklanja se i kardiogena glavobolja.

**Ključne reči:** Migrena, kardiogena glavobolja, sekundarna glavobolja, akutna srčana ishemija

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