

# Orofacial Pain and Toothache as the Sole Symptom of an Acute Myocardial Infarction Entails a Major Risk of Misdiagnosis and Death

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**Aims:** To provide an update of knowledge regarding the clinical presentation and neurophysiologic aspects of orofacial pain of cardiac origin in the form of a literature review. **Methods:** The peer-reviewed databases Scopus/Embase, NCBI (PubMed), and Science Direct were searched up to December 2018. **Results:** Patients with myocardial infarction presenting without chest pain run a higher risk of death due to missed diagnosis and subsequently a significantly greater delay between the onset of symptoms and arrival at the hospital. During myocardial ischemia, orofacial pain is reported by 4 in 10 patients and described as oppressive and/or burning. Up to 4% of myocardial infarction patients experience pain solely in the orofacial structures, women more often than men. Orofacial pain during myocardial ischemia is associated with ischemia within the inferior wall of the heart, suggesting the involvement of the vagal system. **Conclusion:** The clinician's awareness of the full spectrum of clinical characteristics of a myocardial infarction constitutes a key factor in accurate diagnosis. Health care professionals and the general public should be aware of the possibility of myocardial infarction presenting with orofacial pain, toothache, or ear/temporomandibular joint pain as the only symptom. *J Oral Facial Pain Headache* 2020;34:53–60. doi: 10.11607/ofph.2480

**Keywords:** cardiac ischemia, cardiac pain, myocardial infarction, orofacial pain, toothache

Coronary disease remains the leading cause of death in developed countries. Despite advances reached in high-sensitivity diagnostic tests for identifying acute myocardial infarction (MI), a significant number of patients still die due to misdiagnosis and treatment delay.<sup>1–4</sup> Misdiagnosis occurs more frequently in patients with atypical symptoms of MI and especially in the absence of chest pain.<sup>5–7</sup> Even at emergency departments, patients with atypical MI symptoms were found to run a three times–higher risk of death than patients seeking care for chest pain.<sup>5</sup> Apart from atypical symptoms, older age, female gender, and diabetes mellitus can be expected to predict treatment delay.<sup>8</sup> In addition, the patient's own understanding, attitude, and response to initial symptoms are crucial for their readiness to seek care and receive prompt treatment.

A survey of professional reports from an Emergency Care Unit in North America concluded that neither physicians nor nurses had mentioned pain in the throat, face, or teeth as a sole symptom suggestive of an MI diagnosis.<sup>9</sup> However, one study found that throat pain and orofacial pain of cardiac origin were common, occurring in nearly 4 out of 10 patients with cardiac ischemia.<sup>10</sup> Furthermore, in the absence of chest pain, the most common locations of pain of cardiac origin were in the throat, teeth, and ears/temporomandibular regions, and not in the left arm, as has commonly been anticipated.<sup>10</sup> These findings were later confirmed in a different patient population in which the study design was replicated in full.<sup>11</sup> These locations of pain are likely to direct the patient to seek an otorhinolaryngologist, a dentist, or a general physician. Hence, these clinicians can obviously be challenged when these pain locations constitute the only symptom of cardiac ischemia with or without MI.

This review aims to provide updated knowledge about the clinical presentation and characteristics of oral and facial pain of cardiac origin and to bring forth neurophysiologic aspects in order to enhance the clinician's diagnostic ability.

## Materials and Methods

This review was based on the available literature up to December 2018. The databases Scopus/Embase, NCBI (PubMed), Google Scholar, and Science Direct were used. Full-text, peer-reviewed articles were identified relating to the area of cardiac pain referred to the head, face, teeth, and pharynx structures. The following keywords were used: cardiac pain, acute myocardial infarction, referred pain, acute coronary syndrome, and cardiac ischemia, in combination with the terms orofacial pain, toothache, throat, ear, temporomandibular joint, chest pain, headache, trigeminal system, and teeth.

## Results

### Acute Coronary Syndrome

The term acute coronary syndrome (ACS) embraces a diversity of clinical signs and symptoms that are related to acute myocardial ischemia, a condition of insufficient blood flow to the heart muscle.<sup>12</sup> Sometimes, myocardial ischemia progresses to MI, which involves cell death and the release of myocardial necrosis biomarkers such as troponin I and troponin T.<sup>3,12,13</sup>

Two main ACS conditions are described based on clinical presentation, electrocardiographic features, and serum levels of cardiac biomarkers: unstable angina and MI.<sup>14–16</sup> In chronic stable angina, the cardiac symptoms present in a pattern that tends to remain constant over time, while unstable angina presents with new or changing symptoms in a crescendo pattern and can also occur at rest.<sup>15</sup> Biomarkers that are released during MI can be detected by specific tests. Also, ECG changes, with development of pathologic Q waves and ST-T alterations, are usually observed.<sup>13</sup>

### Clinical Presentation of Symptomatic Acute MI

The clinician's awareness of the spectrum of clinical characteristics of MI constitutes a key factor for a prompt and accurate diagnosis. Full assessment of the patient's symptoms, evaluating location, quality, intensity, and duration of pain, is important. Any aggravating, relieving, or radiating factors should be taken into account.<sup>12,13</sup> Cardiac pain is typically localized in the middle and left side of the chest, but can also radiate to the neck, arms, shoulders, stomach,

and jaws.<sup>17,18</sup> The general public tends to recognize oppressive pain in the middle of the chest as a symptom of MI.<sup>19</sup> Other clinical symptoms to take into diagnostic consideration are breathlessness, palpitations, weakness, nausea, sweating, and vertigo.<sup>20</sup>

### MI Presenting Without Chest Pain

The prevalence of MI presenting without chest pain varies between 8% and 30%.<sup>14,21–23</sup> The reported prevalence is likely to constitute an underestimation because the individuals who died before being admitted to the emergency room were not included in the published research data. MI patients without chest pain have a higher mortality rate due to missed diagnosis and a significantly greater delay between the onset of symptoms and arrival at the hospital.<sup>21,24</sup> They are also treated less aggressively and experience higher in-hospital mortality.<sup>25</sup>

Only a few studies have been conducted focusing on myocardial ischemia presenting without chest pain, and several methodologic limitations can be observed. Most of the large studies are retrospective in design and include data from regional,<sup>22</sup> national,<sup>6</sup> and international registries.<sup>23</sup> In these studies, the quality and accuracy of the analyzed data depend on many different clinicians, often from different countries, evaluating the patients without a specific research question and protocol. Other limitations of studies included selection bias; eg, by including subjects from clinical trials<sup>26</sup> or by including only MI patients.<sup>6,22,24,26</sup>

### Orofacial Pain as the Sole Symptom of MI

For a long time, the association between myocardial ischemia and craniofacial pain was mainly published as case reports.<sup>27–36</sup> Toothache, throat pain, jaw pain, temporomandibular joint (TMJ) pain/ear pain, and headache have been the most commonly reported craniofacial pain locations. Misdiagnosis, mistreatment, and delay of appropriate therapy are common findings in these reports.

In one case report, a 71-year-old man with pain in a mandibular first premolar was mistakenly diagnosed as having a dental problem. After endodontic treatment had failed to resolve the pain, the patient was referred for medical diagnostic consultation. An ECG revealed myocardial ischemia, and coronary angiography demonstrated a 90% occlusion of the left anterior descending coronary artery. The missed diagnosis resulted in unnecessary dental treatment, and the patient's life was put at risk.<sup>28</sup> Another case report described a 48-year-old man with no history of systemic disease who complained of severe pain in one ear/TMJ area for 4 months. Examinations of the intraoral structures, TMJs, and nasal sinuses revealed no pathology. In the absence of any clinical or radio-

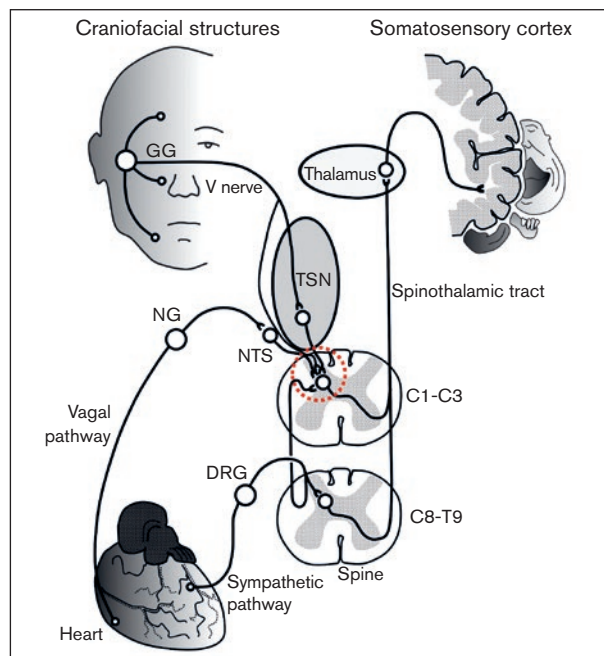
graphic findings and after thorough consideration of pain characteristics, the patient was referred for cardiologic evaluation, and coronary disease was disclosed. After appropriate cardiac surgery, the TMJ pain resolved.<sup>35</sup>

During the last decade, a prospective research project of consecutive patients has addressed the clinical challenge of referred pain of cardiac origin by focusing on its prevalence, the spectrum of clinical presentations, differential diagnosis vs pain induced by odontogenic pathology, the association between the cardiac location of MI and presence of craniofacial pain (with some neurophysiologic implications), and the possibility of craniofacial pain as the sole prodromal symptom of an acute MI.<sup>10,37–39</sup> During myocardial ischemia, pain was experienced in the craniofacial region by 8 in 20 patients (38%). This high incidence was later confirmed by a different research team using the same study protocol to repeat the study in a different patient population. The prevalence then amounted to 7 in 20 patients (34%).<sup>40</sup> Recently, one more study used the outline of the same research protocol to repeat the original prospective study of consecutive patients with cardiac ischemia. However, the material selection—as well as the implementation of different study criteria—display shortcomings, and the results therefore do not allow for comparison to the original study.<sup>41</sup>

A finding of utmost importance was that 40% of MI patients experienced pain only in the orofacial structures; ie, they had none of the commonly acknowledged symptoms such as chest and arm pain.<sup>10</sup> This study also found that women were more commonly affected by craniofacial pain than men, a finding confirmed when the study was repeated.<sup>40</sup>

It was also revealed that the most common sites of pain referral were the upper part of the throat, the left mandible, the left TMJ/ear region, the right mandible, and the posterior teeth.<sup>10</sup> The following part of the project revealed that four pain quality descriptors (aching, burning, pressure, and throbbing) can be helpful in the differentiation of orofacial and throat pain of cardiac origin vs pain at the same sites but of dental origin.<sup>37</sup> When craniofacial pain was the sole symptom of myocardial ischemia, the pain descriptors pressure and/or burning were used by the vast majority of the patients, while odontogenic pain was mainly described as throbbing and aching.<sup>37</sup>

The third part of the project disclosed that the occurrence of orofacial pain during myocardial ischemia was associated with ischemia within the inferior wall of the heart, suggesting the involvement of the vagal system in the mechanisms of oral and facial pain of cardiac origin.<sup>38</sup> Figure 1 shows the plausible neural mechanisms of craniofacial pain referred from the heart.



**Fig 1** Potential mechanisms of craniofacial pain referred from the heart. Schematic drawing based on data from experimental and clinical research illustrating the neurophysiologic mechanisms for craniofacial pain of cardiac origin. Sympathetic, vagal, and trigeminal inputs converge in spinothalamic C1–C3 neurons, which then convey data to the craniofacial areas represented at the cortex level. GG = Gasserian ganglion; NG = Nodose ganglion; DRG = dorsal root ganglion; TSN = trigeminal spinal nucleus; NTS = nucleus tractus solitarius. Reprinted from Kreiner et al (*J Oral Facial Pain Headache* 2014;28:317–321).

**Table 1 Summary of Pain Characteristics for Differential Diagnosis of Different Orofacial Pain Conditions**

Pain characteristics	Dental origin	Cardiac origin	TMJ area pain	TN
Throbbing	Yes	No	No	No
Aching	Yes	No	Yes	No
Suffocating	No	Yes	No	No
Pressure	No	Yes	Rarely	No
Electric	No	No	No	Yes
Burning	No	Yes	No	Rarely
Aggravated by physical activity	No	Yes	No	No
Relieved by rest	No	Yes	No	No

TMJ = temporomandibular joint; TN = trigeminal neuralgia.

In the fourth part of the project, the authors detected that the sequence of events resulting in craniofacial pain as the only symptom of cardiac ischemia was true also for prodromal angina (pre-infarction). Pain in the orofacial structures was the only prodromal symptom of MI in 5% of patients.<sup>39</sup> Table 1 summarizes some characteristics that might help the clinician in the initial clinical diagnosis of symptoms caused by cardiac ischemia with or without MI vs other frequent conditions with pain manifestation in the same locations.

## Orofacial Pain Neurophysiology

**Orofacial Pain.** The trigeminal nerve (V cranial nerve) is the primary nerve responsible for transmitting pain sensations from the face and the intraoral structures. The neural mechanisms of the trigeminal system are very intricate, and this complexity can challenge the clinician in establishing a proper diagnosis and treatment selection. Trigeminally mediated pain may involve peripheral and central mechanisms, which often coexist.

### Peripheral Mechanisms

A-delta and C-afferent trigeminal fibers are responsible for the transmission of nociceptive input from the periphery to the central nervous system. They originate in the craniofacial tissues as pain receptors (nociceptors) that are activated by noxious stimuli. Many chemical mediators are released during tissue injury and participate in the sensitization and activation of the craniofacial nociceptors. Most of the peripheral mediators that have been identified in the spinal system are also involved in nociceptor activation within the peripheral trigeminal system.<sup>42</sup> Substance P, serotonin, histamine, bradykinin, neuropeptide Y, vasoactive intestinal peptide, cytokines, calcitonin gene-related peptide (CGRP), and prostaglandins have all been found to be important peripheral nociceptive mediators in the orofacial tissues.<sup>43–47</sup>

The peripheral mechanisms engaged in the activation of the nociceptors involve complex biochemical interactions. Since several pain medications act at the peripheral level, the understanding of these mechanisms has important clinical implications. Essential nociceptive receptors in the orofacial structures are the free nerve endings. Some of the specific membrane receptors include the G-protein-coupled receptor, the sodium channels, the voltage-gated potassium channels, and the calcium channels.<sup>42</sup> Furthermore, the involvement of glial cells and their mediators has been shown to participate in the peripheral mechanisms of both the genesis and maintenance of pain within the trigeminal system.<sup>48,49</sup> After induction of inflammation in the TMJ area, glial cells become activated in the trigeminal ganglia, suggesting that this phenomenon may be an important factor involved in pain modulation and trigeminal sensitization. Once the pain receptors are activated and the A-delta and C fibers are excited, these afferent fibers conduct the inputs toward the central nervous system into the trigeminal spinal nucleus.

### Central Mechanisms

The central processing of craniofacial pain involves a large number of interactions between neural circuits in the brainstem and other parts of the central

nervous system. The caudal portion of the trigeminal spinal nucleus (subnucleus caudalis) is the main brainstem relay for trigeminal nociceptive inputs.<sup>46</sup> It plays a key role in the integration of somatic and noxious craniofacial inputs. The subnucleus caudalis is the location where the primary nociceptive afferent neurons synapse with the second-order neurons of the nociceptive trigeminal pathway. The main excitatory neurotransmitters involved in this relay are glutamate, substance P, and CGRP.<sup>50–52</sup> Several pain modulation mechanisms are involved within the trigeminal nucleus complex. Inhibitory GABAergic and glycinergic circuits have been described in the trigeminal subnucleus caudalis.<sup>53,54</sup> Several pain conditions within the trigeminal system might be related to alterations of these circuits.<sup>55</sup> Under inflammatory pain conditions, GABAergic receptors were found to participate in pain processing.<sup>56</sup>

Several structures within the central nervous system receive inputs from the trigeminal spinal nucleus. The limbic system, the reticular formation, the thalamus, and the cortex play a major role in the craniofacial processing and perception of nociception.<sup>57,58</sup>

## Cardiac Pain Neurophysiology

**Peripheral Mechanisms.** Data from experimental settings in animals showed that coronary artery occlusion activates cardiac nociceptive afferent fibers.<sup>59</sup> The identification of a specific chemical mediator that initiates nociceptive activation during cardiac ischemia has not been successful. Data suggest that multiple mediators are released at the same time, with possible interactions occurring between them. Some of the peripheral biochemical mediators that are released during myocardial ischemia include bradykinin, thromboxane, adenosine, potassium, histamine, and prostaglandins.<sup>60–64</sup> Bradykinin is believed to be the key mediator of cardiac pain, but its specific role is still not clear.<sup>65</sup> The capacity of bradykinin alone to excite spinal neurons was very similar to the effects evoked by a mixture of algogenic substances, with the main difference being a significantly shorter time to peak and recovery time of long-lasting excitatory neuron responses with bradykinin.<sup>66</sup> Thus, it is plausible that bradykinin plays a key role in cardiac pain in combination with other chemical mediators. In line with this hypothesis, it was found that bradykinin and thromboxane A<sub>2</sub> interact to stimulate ischemia-sensitive cardiac afferent endings, leading to synergistic afferent responses.<sup>63,64</sup>

### Sympathetic and Vagal Mechanisms

Sympathetic afferent fibers are more densely distributed in the anterior wall of the heart, while vagal afferent fibers are more densely distributed in the posterior-inferior wall.<sup>67</sup> This distribution may



influence cardiac pain symptoms during different pathologic conditions. Both vagal and sympathetic systems become activated during myocardial ischemia. While data from surgical interventions showed that sympathetic afferents contribute to most of the pain generated during angina pectoris, angina pain in the neck and jaws persisted after sympathectomies.<sup>68</sup> Thus, vagal afferents are also involved in cardiac pain processing. Vagal involvement was shown in experimental studies, mainly in relation to the inferior-posterior surface of the heart and to pain referral to the jaws and the neck.<sup>69–71</sup>

The cell bodies of the sympathetic afferents from the heart are located in the dorsal root ganglia, between C8 and T9. The afferent axons enter the gray matter and are more densely distributed in the T2–T6 segments.<sup>72</sup> The cell bodies of the cardiac vagal afferent fibers are located in the ganglion nodosum, from which they can reach the upper spinal cord.<sup>73</sup> It has been hypothesized that these projections involve a connection within the nucleus tractus solitarius.<sup>66,70</sup> The ascending pathways for cardiac nociceptive inputs involve both the spinothalamic and the spinoreticular tracts.<sup>65</sup>

### **Mechanisms of Cardiac Pain Referred to the Craniofacial Region**

Pain referral from the heart to the trigeminal system involves neural mechanisms such as central convergence of cardiac nociceptive inputs and central sensitization within the trigeminal system and the upper cervical spine.<sup>38,68</sup> Experimental data points to the involvement of convergence mechanisms at the upper cervical spine segments where trigeminal, visceral, and phrenic inputs converge.<sup>74</sup> In line with these findings, it was shown that the trigeminal subnucleus caudalis receives extensive convergence inputs from cutaneous, muscular, and visceral afferents.<sup>75</sup>

A modulatory action of cardiac inputs into the trigeminal system, as well as a connection between cardiac vagal afferents and trigeminal and trigemino-thalamic neurons, has been shown.<sup>76</sup> Data from experimental studies in animals suggest a plausible explanation for a potential neurophysiologic mechanism that may explain referred pain to the face during myocardial ischemia. In fact, the excitatory effect of cardiac nociceptive afferent fibers on C1–C3 neurons, which also receive somatic inputs from the craniofacial structures, has been shown.<sup>69,71</sup> More support for this hypothesis was given when it was shown that 89% of C1–C2 spinal neurons, which respond to intrapericardial algogenic substances, are also excited by mechanical stimulation of the craniofacial structures innervated by trigeminal afferent fibers.<sup>71</sup>

The detailed involvement of vagal and sympathetic inputs from the heart to C1–C2 neurons is still not

well known. However, research data strongly suggest that cardiac vagal afferents specifically contribute to jaw and neck pain more than sympathetic afferent fibers. This assumption is based on the finding that spinothalamic tract neurons in C1–C2 related to somatic fields in the jaws and the neck were more reactive to vagal than to sympathetic experimental electrical stimulation.<sup>69,77</sup> The hypothesis suggesting a neural connection between cardiac vagal inputs and spinothalamic C1–C2 neurons is also supported by one study that found transection of the vagus nerve eliminated the neural activity at C1–C2 neurons, which was elicited by the injections of algescic substances in the pericardium.<sup>71</sup>

The hypothesis that there is a vagal involvement in craniofacial pain of cardiac origin is also supported by clinical data. These emerged from the side effects of a Vagus nerve stimulator (VNS), an electrical device implanted in the chest and attached to the left Vagus nerve.<sup>78</sup> One case report described a patient who developed left-sided toothache after the implantation of a VNS, with episodes of pain that were intermittent and coincided with the duration of the VNS stimulus (30 seconds every 5 minutes).<sup>79</sup> Other case reports have also described toothache and facial pain as a side effect of VNS in previously asymptomatic patients.<sup>80,81</sup>

### **Diagnostic Concerns and Considerations**

In some instances, local anesthetic can assist in differential diagnosis. Local anesthesia of the painful area can be diagnostic when the clinicians suspect that oral and facial pain is heterotopic; ie, referred from another site such as facial muscles, TMJs, or the cardiac muscle. If the pain originates from the site of injection, pain will be reduced or eliminated. Should the injection fail to reduce the pain, pain referral must be considered. Pain referral is relatively common in the head and neck, cardiac pain being only one of several possible sources. Should the pain be of cardiac origin, the patient is potentially at risk. Further investigation is therefore necessary to determine whether the cardiac muscle should be considered the source of the pain referral. Table 1 can assist the clinician at the primary clinical examination.

It is important to note that many local anesthetics contain vasoconstrictors. When the clinician has reason to suspect that the pain is referred from the cardiac muscle, local anesthetics containing a vasoconstrictor should be avoided because injection of a vasoconstrictor is likely to aggravate a coronary occlusion and place the patient at additional risk.

An additional diagnostic consideration is the use of vasodilating medication such as sublingual nitroglycerine. This medication should only be prescribed by clinicians who are familiar with the potential

adverse side effects. If the patient is already under cardiovascular supervision, they may have sublingual nitroglycerine tablets already prescribed and available. If that is the case and cardiac ischemic pain referral is strongly considered, the patient can place a tablet under the tongue to determine the effect on the craniofacial pain. If the pain is reduced, cardiac ischemic pain is confirmed, and an immediate referral to an appropriate health care provider is indicated.

## Conclusions

Early recognition of MI followed by prompt therapy can play a critical life-saving role. Health care professionals and the general public should be aware of the possibility of cardiac ischemia and acute MI presenting as throat pain, toothache, or facial pain as the only symptom. Clinical characteristics such as pain provocation or aggravation by physical or psychologic stress, an oppressive or burning quality of pain, and symptom amelioration with rest should alert the clinician to this possibility. In such situations, the patient should be immediately referred for urgent cardiologic evaluation.

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