

# Craniofacial Pain of Cardiac Origin Is Associated with Inferior Wall Ischemia

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**Aims:** To investigate possible associations between the presence of craniofacial pain of cardiac origin and the location of cardiac ischemia and conventional risk factors. **Methods:** A total of 326 consecutive patients with confirmed myocardial ischemia (192 males, 134 females, mean age 64 years) were studied. Demographic details, health history, risk factors, prodromal symptoms, electrocardiogram (ECG) findings, and pain characteristics during the ischemic episode were assessed. The location of the ischemia according to the ECG findings was categorized as anterior, inferior, or lateral. Univariate chi-square analyses and a multivariate logistic regression model were used for data analysis. Two age subgroups (< 65 and > 65) were established when controlling for covariates. **Results:** Craniofacial pain of cardiac origin was significantly associated with an inferior localization of cardiac ischemia ( $P < .001$ ) and was more frequently reported in diabetic patients ( $P = .014$ ). Thirty-eight patients (12%) did not experience chest pain during the myocardial ischemia. Nine patients (3%) experienced a prodromal angina episode without chest pain. **Conclusion:** The occurrence of craniofacial pain during myocardial ischemia, with or without an acute myocardial infarction, was associated with ischemia within the inferior wall. This result suggests the involvement of the vagal afferent system in the mechanisms of craniofacial pain of cardiac origin. *J Oral Facial Pain Headache* 2014;28:317–321. doi: 10.11607/ofph.1257

**Key words:** acute myocardial infarction, cardiac ischemia, chest pain, craniofacial pain, dental pain

**A**cute myocardial infarction (AMI) presenting without chest symptoms puts patients at high risk. Hence, AMI patients who do not experience chest pain have a significantly greater delay between the onset of symptoms and arrival at a hospital for treatment.<sup>1</sup> They are more often misdiagnosed, are less likely to receive appropriate therapy, and have, as a consequence, a higher risk of death.<sup>1–9</sup>

One explanation for misdiagnosis is highlighted in previous findings that in patients with no chest pain during myocardial ischemia, craniofacial pain prevailed over pain occurring in other well-recognized referral sites, such as the arms or shoulders, and nearly half of these patients reported only craniofacial pain during the ischemic episode.<sup>10</sup> Since early recognition of this high-risk group should improve survival, there is a need for greater understanding of atypical symptom presentation during myocardial ischemia, including prodromal (preinfarction) angina.

Experimental animal studies have provided evidence of a neural mechanism of pain that originates in the heart but is experienced in the neck and head.<sup>11–13</sup> These findings support the clinical observation, which was limited to AMI patients, of an association between the infarction location in the inferior wall of the heart and pain referred to the neck and jaws.<sup>14</sup>

Since AMI patients without chest pain form a high-risk group, this study aimed to investigate possible associations between the presence of craniofacial pain of cardiac origin and the location of cardiac ischemia and conventional risk factors. An additional objective was to investigate whether there was any association between the location of the myocardial ischemia and the presence or absence of chest or craniofacial pain,

**Table 1 Associations Between Groups and the Analyzed Covariates**

	Myocardial ischemia (n = 326)				
	With chest pain n = 288 (88%)	Without chest pain n = 38 (12%)	P value	Odds ratio (95% CI)	With CFP n = 126 (39%)
Hypertension	n = 203 (70%)	n = 24 (63%)	.456	0.75 (0.36–1.57)	n = 86 (68%)
Diabetes mellitus	n = 87 (30%)	n = 8 (21%)	.314	0.64 (0.27–1.51)	n = 47 (37%)
Smoking	n = 154 (53%)	n = 26 (68%)	.246	1.57 (0.73–3.35)	n = 64 (51%)
Family history of CAD	n = 137 (47%)	n = 16 (42%)	.673	0.85 (0.42–1.74)	n = 69 (55%)
Hypercholesterolemia	n = 183 (63%)	n = 26 (68%)	.329	1.45 (0.68–3.11)	n = 88 (70%)
Obesity	n = 108 (37%)	n = 13 (34%)	.865	0.93 (0.45–1.95)	n = 42 (33%)
Anterior ischemia*	n = 176 (61%)	n = 17 (45%)	.331	0.62 (0.24–1.61)	n = 69 (55%)
Inferior ischemia*	n = 113 (39%)	n = 18 (47%)	.918	1.04 (0.41–2.64)	n = 66 (52%)
Lateral ischemia*	n = 93 (32%)	n = 14 (37%)	.559	1.28 (0.55–2.97)	n = 36 (29%)

\*Location alone or in combination.

CFP = craniofacial pain; CAD = coronary artery disease; CI = confidence interval.

P values in bold indicate statistical significance.

based on the hypothesis that craniofacial pain would be associated with myocardial ischemia occurring in those areas more densely innervated by vagal afferent fibers, ie, the inferior wall of the heart.

## Materials and Methods

### Study Population

A total of 326 consecutive patients with confirmed symptomatic myocardial ischemia (192 males, 134 females, mean age 64 years) were derived from 384 patients admitted with signs and/or symptoms of myocardial ischemia to three cardiology units in Montevideo, Uruguay. Patients who were excluded did not meet the inclusion criteria; ie, myocardial ischemia was not verified (n = 25); craniofacial pain was from verified noncardiac sites of origin (n = 18); ischemia was asymptomatic (n = 9); or the patient was diagnosed with severe heart failure (n = 3), psychiatric disorders, or confusion (n = 3). The Ethics Committees at the Universidad de la República and the Hospital Central de las Fuerzas Armadas, Uruguay, approved the study protocol. Informed consent was obtained from each included patient.

Myocardial ischemia, AMI, and location of ischemia were diagnosed by cardiologists according to the American College of Cardiology definitions.<sup>15</sup> The examination and interview methods are described in detail elsewhere.<sup>10,16</sup> In summary, data were collected on demographic details, health history, risk factors, prodromal symptoms, and electrocardiogram (ECG) findings on the locations of ischemia and pain during myocardial ischemic episodes. The cardiac locations based on the ECG findings were categorized as anterior (leads V1 to V4), inferior (leads II, III, aVF), or

lateral (leads I, aVL, V5 to V6) according to established criteria.<sup>15</sup> Ischemia-related symptoms that were experienced within 5 months prior to the occurrence of an AMI were regarded as prodromal.<sup>17,18</sup>

### Data Analysis

Univariate chi-square analyses were used to assess differences in symptom presentation between groups. A multivariate logistic regression model was used to analyze possible associations between the absence of chest pain, presence of craniofacial pain (dependent variables) and age, sex, risk factors, and location of ischemia. Two age subgroups (< 65 and > 65) were established when controlling for covariates in the logistic regression models. The Wilcoxon test was used to compare mean ages between groups. The “R” software was used to perform the statistical analysis.<sup>19,20</sup>

## Results

The multivariate logistic regression analysis showed that the occurrence of craniofacial pain of cardiac origin was significantly associated with an inferior localization of the myocardial ischemia ( $P < .001$ ) (Table 1), even without an AMI ( $P = .005$ ) and was significantly more frequently reported in women ( $P = .033$ ). There was no correlation between the absence of chest pain and the analyzed covariates of age, sex, conventional risk factors (hypertension, diabetes mellitus, smoking, family history of coronary artery disease, hypercholesterolemia, and obesity) or location of ischemia. However, the occurrence of craniofacial pain during myocardial ischemia was significantly associated with diabetes ( $P = .014$ ) and family history of coronary artery disease ( $P = .032$ ). There were no

Without CFP n = 200 (61%)	P value	Odds ratio (95% CI)
n = 141 (70%)	.372	0.78 (0.46–1.33)
n = 48 (24%)	<b>.014</b>	1.93 (1.18–3.15)
n = 116 (58%)	.361	0.79 (0.48–1.30)
n = 84 (42%)	<b>.032</b>	1.70 (1.03–2.79)
n = 121 (61%)	.215	1.37 (0.83–2.27)
n = 79 (40%)	.116	0.67 (0.41–1.10)
n = 124 (62%)	.666	1.13 (0.63–2.03)
n = 65 (33%)	<b>&lt;.001</b>	2.40 (1.36–4.24)
n = 71 (36%)	.449	0.81 (0.48–1.37)

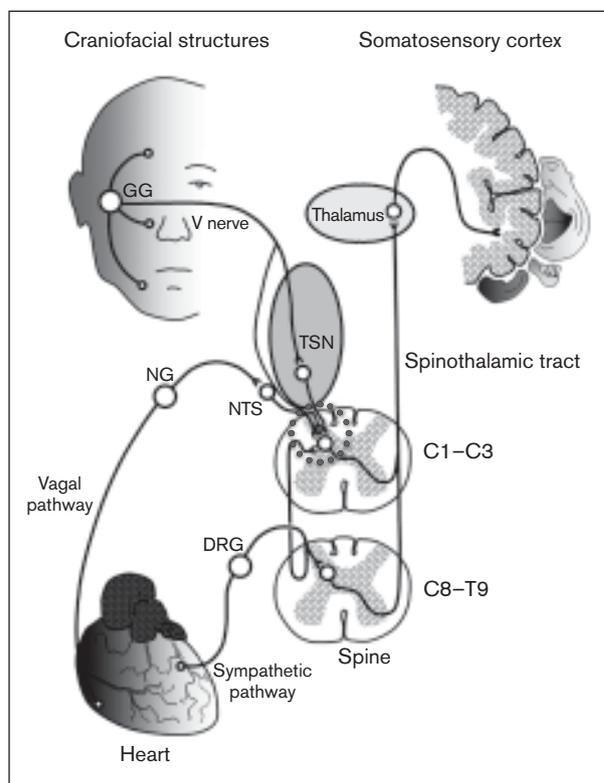
differences between patients with and without chest pain or with and without craniofacial pain regarding mean age or AMI prevalence.

No differences were found for any variable when the data categorizing the patients into two age subgroups (< 65 and > 65) were analyzed. Thirty-eight patients (12%) did not experience chest pain during the myocardial ischemic episode. AMI was experienced by 120 patients (39 women and 81 men, mean age 63 years), and 18 of them (15%) did not report any chest symptoms. Nine AMI patients experienced a prodromal angina episode without chest pain.

The most frequently reported craniofacial pain locations during cardiac ischemia were the throat, the left mandible, the right mandible, the left temporomandibular joint/ear region, and the posterior teeth. The pain quality descriptors “pressure” and “burning” were the most frequently used by patients when describing the facial pain from cardiac origin. These results are consistent with previous reports.<sup>10,16</sup>

## Discussion

This study has shown an association between the occurrence of craniofacial pain and an inferior location of the myocardial ischemia. This finding lends support to a previously reported association between an inferior ischemic location in the heart wall and neck and jaw pain in patients with an AMI.<sup>14</sup> While Culic et al<sup>14</sup> only investigated patients with an AMI, the present study found the same association in patients with myocardial ischemia with or without an AMI. Since vagal afferent fibers are densely distributed in the posterior-inferior wall of the heart,<sup>21</sup> the clinical association found in the present study points to a potential



**Fig 1** Hypothetical mechanism of craniofacial pain referred from the heart. Schematic drawing based on data from experimental and clinical research. Sympathetic, vagal, and trigeminal inputs converge in spinothalamic C1–C3 neurons, which then convey signals to the craniofacial areas represented at the somatosensory cerebral cortex level. GG = gasserian ganglion; NG = Nodose ganglion; DRG = dorsal root ganglion; TSN = trigeminal spinal nucleus; NTS = nucleus tractus solitarius. Grey dotted circle = convergence zone of inputs.

involvement of the vagal afferent system in the mechanisms of craniofacial pain of cardiac origin (Fig 1).

Experimental data from animal studies show that spinothalamic tract neurons in C1–C2, which are related to somatic fields in the jaws and the neck, are more reactive to vagal than to sympathetic experimental electrical stimulation,<sup>22,23</sup> providing support to this view. The postulated neural connection between cardiac vagal inputs and spinothalamic C1–C2 neurons gained support when 6% of the neurons from the vagal nodose ganglion were found to project to the upper cervical spinal cord.<sup>24</sup> The neural activity of C1–C2 neurons, which could be elicited by injections of algescic substances into the pericardium, was eliminated by transection of the vagus nerve.<sup>12,13</sup> A possible vagal involvement in craniofacial pain of cardiac origin is also supported by clinical observations. 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, which is used to treat intractable depression and some types of refractory epilepsy.<sup>25</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>26</sup> Other case reports have also described toothache and facial pain as a side effect of VNS in previously asymptomatic patients.<sup>27,28</sup>

Thus, although sympathetic afferents play a major role in conveying anginal pain, vagal involvement appears critical for afferent nociceptive conduction from the inferior-posterior region of the heart and in the referral of pain to the craniofacial area.<sup>13,22,29,30</sup> A previous report by the present authors showed that in the absence of chest pain, any other pain during acute episodes of myocardial ischemia is more frequently referred to the craniofacial area than to well-recognized referral sites such as the arms or shoulders.<sup>10</sup> These findings were reinforced by the present results, now based on a larger population of patients. In addition, it was found that this frequency of pain referral to the craniofacial area also occurred in preinfarction angina.

In the present study, the prevalence of AMI presentation without chest pain was 15%. It is noteworthy that in previous studies, this prevalence varied considerably, between 8% and 30%.<sup>3,4,6,7</sup> Several methodological reasons may explain this difference. Firstly, most of the large studies focusing on this topic were retrospective in design and included data collected from regional, national, or international registries.<sup>7,6,31–33</sup> This type of design implies that the quality and accuracy of the analyzed retrospective data depended on many different clinicians, often from different countries, and that the patients were evaluated in the absence of a specific research question and protocol. Secondly, the lack of homogeneity between definitions of the chest pain groups makes study comparisons difficult and may explain the large differences between their results. In one report, the chest pain group consisted of patients who had chest pain as the “predominant” presenting symptom,<sup>7</sup> meaning that the non-chest pain group may have had chest symptoms that were not “predominant,” while in another study<sup>32</sup> the chest pain group was defined as “. . . any symptom of chest discomfort, sensation or pressure, or arm, neck, or jaw pain . . .” This definition may imply that patients with neck or jaw pain alone would have been included in the chest pain group, making the results difficult to interpret.

The present study also revealed a statistically significant association between the presence of craniofacial pain during myocardial ischemia and diabetes. This finding is in line with previous research that showed diabetes is associated with atypical symptom presentation of ischemic heart disease, including

pain location.<sup>33,34</sup> One study reported that younger adults with diabetes run a 2.5-fold higher risk of experiencing atypical symptoms during an acute coronary event than do the younger adults without diabetes.<sup>34</sup> However, the present study did not find any statistical differences in the occurrence of craniofacial pain when it compared younger and older adults with diabetes.

While this study analyzed associations related to specific ECG changes, it is important to note that about 7% of AMI patients present with normal or nonspecific ECGs.<sup>35</sup> However, this group of patients does not have a higher in-hospital mortality rate compared to patients with specific ECG changes.<sup>35</sup>

## Conclusions

These findings add new data to the existing knowledge of pain of cardiac origin. The association found between the occurrence of craniofacial pain and inferior wall ischemia strongly suggests the involvement of the vagal afferent system in the mechanisms of craniofacial pain referred from the heart. Further research is needed to understand better these clinical and neurophysiological interactions.

## Acknowledgments

The research was funded by the Universidad de la República (CSIC), Uruguay, the Medical Faculty, Umeå University, Sweden, and the Swedish Dental Society. The authors thank the Instituto Nacional de Cirugía Cardíaca (INCC) for its valuable participation in the study, and they are grateful to Rachel Nicoll, medical writer, for her thorough language review of the paper and her constructive criticism and to Dr Alejandro Ferreira for his constructive criticisms. The authors report no conflicts of interest related to this study.

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