Umeå University Medical Dissertations
New Series No 117, ISSN:0345-7532, ISBN:978-91-7459-160-6

# Craniofacial Pain of Cardiac Origin

An Interdisciplinary Study

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SWEDEN

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ISBN: 0345-7532
ISSN: 978-91-7459-160-6
Front cover: Fredrik Bryndahl
Back cover: Fabian Mowszowicz
Printed by: Arkitektkopia, Umeå, 2011
Umeå, Sweden 2011

Learning never exhausts the mind.

*Leonardo da Vinci (1452-1519)*

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# PREFACE

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. Kreiner M, Okeson JP, Michelis V, Lujambio M, Isberg A. Craniofacial pain as the sole symptom of cardiac ischemia. A prospective multicenter study. J Am Dent Assoc 2007;138:74-79.

II. Kreiner M, Falace D, Michelis V, Okeson JP, Isberg A. Quality Difference in Craniofacial Pain of Cardiac vs. Dental Origin. J Dent Res 2010;89:965-969.

III. Kreiner M, Alvarez R, Michelis V, Waldenström A, Isberg A. Craniofacial pain can be the sole prodromal symptom of an acute myocardial infarction. An interdisciplinary study. Manuscript.

IV. Kreiner M, Alvarez R, Michelis V, Waldenström A, Muñiz R, Isberg A. Craniofacial pain of cardiac origin is associated with inferior wall ischemia. Manuscript.

# ABSTRACT

Referred pain is frequently associated with misdiagnosis and unnecessary therapy directed to the pain location instead of its origin. When craniofacial pain is the sole symptom of myocardial ischemia, failure to recognize its cardiac source can endanger the patient. In particular, patients with acute myocardial infarction (AMI) who do not experience chest pain run a very high risk of misdiagnosis and death. Pain that is limited to the craniofacial region during myocardial ischemia has so far been described only in case reports and its overall prevalence is unknown. Experimental research in animals suggests a vagal involvement in the pathological mechanisms of cardiac pain referred to the face.

The aim of this study was to gain knowledge about the prevalence, clinical characteristics and possible mechanisms of craniofacial pain of cardiac origin, in order to improve the clinician's ability to make a correct diagnosis. It was hypothesized that the quality of craniofacial pain from cardiac versus dental origin would differ, implying a high diagnostic validity. It was also hypothesized that craniofacial pain can be the sole symptom of a prodromal (pre-infarction) angina episode and that this pain location would be especially associated with cardiac ischemia in the areas more densely innervated by vagal afferent fibres.

The study group was comprised of consecutive patients who experienced craniofacial pain of a verified cardiac (n=326) or dental (n=359) origin. Demographic details on age, gender and pain characteristics (location, quality and intensity) were assessed in both groups. Cardiovascular risk factors, cardiac diagnosis and ECG signs of ischemia were also assessed in the cardiac pain group. Ethics approval and informed consent for each patient was obtained.

Craniofacial pain was found to be the sole symptom of myocardial ischemia in 6% of patients and was the sole symptom of an AMI in 4% of patients; this craniofacial pain was more prevalent in women ($p=0.031$). In those patients without chest pain, it was the most frequent pain location and was the only symptom of prodromal angina

in 5% of AMI patients. The craniofacial pain included the throat, the jaws, the temporomandibular joints/ears and the teeth, mainly bilaterally. The pain quality descriptors “pressure” and “burning” were statistically associated with pain of cardiac origin, while “throbbing” and “aching” were associated with an odontogenic cause ($p<0.001$). In myocardial ischemia patients, the occurrence of craniofacial pain was associated with an inferior localization of ischemia in the heart ($p<0.001$).

In conclusion, this study showed that pain in the craniofacial region could be the sole symptom of cardiac ischemia and AMI, particularly in women. Craniofacial pain of cardiac origin was commonly bilateral, with the quality pain descriptors “pressure” and “burning”, and pain provocation with physical activity and pain relief at rest. The association between the presence of craniofacial pain and inferior wall ischemia suggests a vagal involvement in the mechanisms of cardiac pain referred to the craniofacial region. Since the possibility of misdiagnosis and death in this group of patients is high, awareness of this clinical presentation needs to be brought to the attention of researchers, clinicians and the general public.

**Key words:** *Acute myocardial infarction, myocardial ischemia, craniofacial pain, referred pain.*

# ABBREVIATIONS

| | |
|---|---|
| AMI | Acute myocardial infarction |
| ACS | Acute coronary syndrome |
| CI | Confidence interval |
| CFP | Craniofacial pain |
| DRG | Dorsal root ganglion |
| ECG | Electrocardiogram |
| GG | Gasserian ganglion |
| NG | Nodose ganglion |
| NTS | Nucleus tractus solitarius |
| TMJ | Temporomandibular joint |
| TSN | Trigeminal spinal nucleus |
| VNS | Vagus nerve stimulator |
| WHO | World health organization |

# INTRODUCTION

Referred pain, the experience of pain in a location which is distant from its source, is a common phenomenon and can present a considerable challenge to clinicians. Failure to diagnose the true cause of referred pain can lead to treatment delay and unnecessary therapy directed to the pain location instead of its real origin and, in the case of referred pain prior to a myocardial infarction, could be life-threatening.

Referred pain within the craniofacial area can be generated by several conditions; odontogenic, myofascial and temporomandibular joint pains are well-documented examples of pain conditions that often present with a referred pain pattern. Although several studies have reported on the prevalence and characteristics of pain in different locations during myocardial ischemia (Everts et al., 1996; Goldberg et al., 1998; Herlitz et al., 1998; Goldberg et al., 2000; Philpot et al., 2001), pain in the craniofacial structures as the sole or main symptom of myocardial ischemia has not so far been well-documented, although there are several case reports (Batchelder et al., 1987; Takayanagi et al., 1990; Rothwel, 1993; Ishida et al., 1996; Kreiner and Okeson, 1999). Despite these case reports, the possibility of referred craniofacial pain being the sole symptom of myocardial ischemia has not been studied in dental and cardiovascular research; as a result, clinicians' awareness that craniofacial pain could be the only symptom of myocardial ischemia is low (Then et al., 2001).

Even though coronary disease is the leading cause of death in developed countries, its clinical and epidemiological characteristics are not yet fully understood, with the risk of both clinicians and the general public being unaware of certain atypical presentations. While there is general recognition among clinicians that atypical presentation of acute myocardial infarction (AMI) is a common occurrence, one study found that craniofacial pain was not mentioned either by physicians or by nurses in an Emergency Care Unit in North America as the only symptom that would suggest an AMI diagnosis (Then et al., 2001). In line with this data, a significant number of patients with atypical symptoms of acute coronary disease die before receiving appropriate hospital care as a result of missed diagnosis and treatment delay (McCarthy et al., 1993; Pope et al., 2000). The difficulty in correctly

recognizing an AMI is reflected in the reported frequency of missed diagnoses found in emergency rooms and outpatient settings, which can be as high as 27% (McCarthy et al., 1993; Chan et al., 1998; Pope et al., 2000; Jaffery et al., 2009). One fourth of missed diagnoses were found to result in fatal or potentially fatal complications for the patient (McCarthy et al., 1993). Furthermore, patients who experience an AMI with atypical symptoms are more likely to be misdiagnosed and discharged from emergency departments than patients with typical presentations (Pope et al., 2000). Early treatment of acute coronary disease plays a critical role in improving outcome. In fact, reperfusion therapy within the early phase of an AMI has been shown to significantly reduce the in-hospital mortality of patients (Kalla et al., 2006) and each 30-minute delay was associated with an increased relative risk of 1-year mortality (De Luca et al., 2004).

Similarly in dental practice, approximately 1% of medical emergencies result in patient death and are mostly associated with acute cardiac failure (Atherton et al., 1999). The estimated risk for British dentists encountering a patient death at sometime during a 40-year career is between 1:12 and 1:19 (Atherton et al., 1999).

## Craniofacial pain: neurophysiologic considerations

The craniofacial region is the focus of complex and debilitating pain conditions. The trigeminal nerve (V cranial nerve) is for the major part responsible for transmitting pain sensations from the face and the complexity of its neurophysiology, involving both peripheral and central mechanisms, may, in part, explain the difficulty which clinicians may experience in understanding and diagnose some conditions.

### *Peripheral mechanisms*

The trigeminal nerve divides in three branches: the ophthalmic ($V^1$), the maxillary ($V^2$) and the mandibular ($V^3$) nerves. The primary afferent fibers of those branches comprise myelinated (A-beta, A-delta) and unmyelinated (C) fibers. A-delta and C afferent fibers are responsible for the transmission of nociceptive input from the periphery to the central nervous system and originate in the craniofacial tissues as pain receptors (nociceptors), which are free

nerve endings that are activated by noxious stimuli. The cell membrane has several types of ion channels and membrane molecules that allow these nociceptors to differentiate between the different types of mechanical, thermal and chemical stimuli.

Several chemical mediators are released during tissue injury and participate in the sensitization and activation of the craniofacial nociceptors. Most of the peripheral mediators which have been identified in the spinal system are also involved in nociceptor activation within the trigeminal system (Henry and Hargreaves, 2007). Substance P, serotonin, histamine, bradykinin, neuropeptide Y, vasoactive intestinal peptide, cytokines, calcitonin gene-related peptide and prostaglandins are the most important peripheral mediators identified in the orofacial tissues (Johansson et al., 1986; Kopp, 1998; Sessle, 2001; Sessle, 2005; Park et al., 2010).

The peripheral mechanisms involved in the activation of the nociceptors involve complex biochemical interactions between the chemical mediators and several types of membrane receptors. The understanding of these physiological interactions has important clinical implications because several pain medications act at this peripheral level. The most important membrane receptors or channels in the orofacial free nerve endings include the G-protein-coupled receptor, the sodium channels, the voltage-gated potassium channels and the calcium channels (for review see Henry and Hargreaves, 2007). Furthermore, a recent study has shown the involvement of glial cells and their mediators which participate in the peripheral mechanisms of both the genesis and the maintenance of pain within the trigeminal system (Villa et al., 2010). After induction of inflammation in the temporomandibular joint area, several 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 action potentials towards the central nervous system. The cell bodies of the primary afferent neurons are located in the Gasserian ganglion, where they have an axon that conducts the nociceptive input into the brainstem and projects into the trigeminal spinal nucleus (See Fig. 1, page 17).

### *Central mechanisms*

The central processing of craniofacial pain is very intricate and involves a large number of neural circuits and interactions within the brainstem and other parts of the central nervous system. The trigeminal spinal nucleus plays a major role in the integration of noxious craniofacial inputs, with the main peripheral afferent contribution coming from the trigeminal fibers. A small number of fibers also converge from the facial, glossopharyngeal and vagus nerves (Capra and Dessem, 1992). The most caudal portion of the spinal nucleus is called the sub-nucleus caudalis and is the main brainstem relay for trigeminal nociceptive inputs (for review see Sessle, 2005). The sub-nucleus caudalis is the location where the primary nociceptive afferent neurons synapse with the second order neuron of the nociceptive trigeminal pathway. The main excitatory neurotransmitters involved in this relay are glutamate, substance P and calcitonin gene-related peptide (Sessle, 2000; Li et al., 2003; Hegarty et al., 2010). Several pain modulation mechanisms are involved within the trigeminal nucleus complex. Inhibitory GABAergic and glycinergic circuits have been described in the trigeminal sub-nucleus caudalis (Avendaño et al., 2005; Bae et al., 2005); alterations of these circuits may play an important role in several pain conditions within the trigeminal system (Martin et al., 2010).

From the trigeminal spinal nucleus, the nociceptive inputs project and ascend into several sites within the central nervous system, including the limbic system, the reticular formation and the thalamus. Projections into the thalamus play a major role in craniofacial pain perception, as several thalamic nuclei act as a relay for ascending nociceptive inputs to the sensory cortex (Lechner et al., 1993; Guy et al., 2005). Projections from the trigeminal spinal nucleus to the ventro-postero-medial thalamic nucleus were found in experimental research to be a major pathway for craniofacial nociceptive information (Guy et al., 2005).

## Cardiac pain: neurophysiological considerations

### *Peripheral mechanisms*

In experimental settings, coronary artery occlusion was shown to activate cardiac nociceptive afferent fibers (Thorén, 1976). Attempts to

identify a specific mediator, which can initiate nociceptive peripheral activation, have not been successful. Therefore, it is likely that multiple mediators are released at the same time and there may be interaction between them. Some of the peripheral biochemical changes that occur during myocardial ischemia include concentration adjustments in bradykinin, thromboxane, adenosine, potassium, histamine and prostaglandins (Hashimoto et al., 1977; Hirsh et al., 1981; Edlund et al., 1983; Fredholm and Sollevi, 1986; Fu et al., 2005; Fu et al., 2008; Fu and Longhurst, 2010). Bradykinin was believed to be the most important mediator of cardiac pain (Baker et al., 1980; Blair et., 1982) but its' specific role is still not clear. 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 (Qin et al., 2009). This data supports the hypothesis that bradykinin plays a key role in cardiac pain in concert with other chemical mediators. In line with these findings, it was recently discovered that bradykinin and thromboxane A2 interact to stimulate ischemia sensitive cardiac afferent endings leading to synergistic afferent responses (Fu et al., 2008; Fu and Longhurst, 2010).

Adenosine was found to be an important mediator of angina pectoris (Sylvén et al., 1987). Coronary sinus concentrations of adenosine are elevated following myocardial ischemia and intravenous administration of adenosine was associated with angina pectoris-like pain in healthy volunteers (Remme et al., 1986; Sylvén et al., 1989). Angina-like chest pain provoked by intravenous and intracoronary injections of adenosine was reported by cardiac patients to be of the same quality as their habitual angina (Lagerqvist et al., 1990; Lagerqvist et al., 1992). Potassium concentrations have been shown to be affected in angina pectoris. Extracellular potassium concentration in myocardial tissue rapidly increases after myocardial ischemia (Webb et al., 1987), although the potassium release during ischemia is often within physiological ranges and may therefore not be sufficient to induce angina. Histamine also contributes to nociceptive activation of cardiac afferents during myocardial ischemia, mainly through the activation of H1 receptors (Fu et al., 2005).

## *Sympathetic and vagal mechanisms*

Both sympathetic and vagal afferent fibers are activated after myocardial ischemia. While there is a significant anatomic overlapping of vagal and sympathetic fibers in the heart, data from histochemical and experimental studies shows that sympathetic afferent fibers are more densely distributed in the anterior wall while vagal afferent fibers are more densely distributed in the posterior-inferior wall of the heart (Quigg et al., 1988; Quigg, 1991; Kawano et al., 2003). This distribution of afferent vagal and sympathetic fibers may influence cardiac pain symptoms during different pathologic conditions.

Data from surgical interventions shows that sympathetic afferents contribute to most of the pain generated during angina pectoris, although after sympathectomies, angina pain in the neck and jaw was not completely eliminated (For review see Foreman and Qin, 2009), suggesting that vagal afferents might also be involved in cardiac pain transmission. During the last decades, experimental studies have shown a strong vagal involvement, mainly in relation to the inferior-posterior surface of the heart and to pain referral to the jaws and the neck (Meller and Gebhart, 1992; Chandler et al., 1996; Foreman, 1999; Qin et al., 2001).

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 grey matter and are more densely distributed in the T2-T6 segments, terminating in lamina I, lamina V and the intermedio-lateral nucleus (Kuo et al., 1984). A-delta and C cardiopulmonary sympathetic afferent fibers excite thoracic and cervical spinothalamic tract neurons (Blair et al., 1981; Chandler et al., 1996).

The cell bodies of the cardiac vagal afferent fibers are located in the ganglion nodosum. These neurons have a distal or peripheral process that connects with the heart and a proximal or central process projecting into the central nervous system. The vagal inputs also reach the upper spinal cord projecting from the nodose ganglion (McNeill et al., 1991). It has been speculated that these projections most probably involve a connection with the nucleus tractus solitarius, which projects to the upper cervical segments (Foreman, 1999; Foreman and Qin, 2009).

The ascending pathways for cardiac nociceptive inputs are constituted by several tracts. Data from experimental studies suggests that the main ascending systems are the spinothalamic and the spinoreticular tracts, which conduct afferent information to the brain (Blair et al., 1984).

## Mechanisms of cardiac pain referred to the craniofacial region

The neural mechanisms involved in craniofacial pain which originates in the heart are still not well understood. Central convergence of cardiac nociceptive inputs into the trigeminal system and the upper cervical spine and central sensitization mechanisms are likely to be involved (Foreman and Qin, 2009). Experimental data points to the involvement of convergence mechanisms at the upper cervical spine segments as it was shown that this is a convergence area for trigeminal, visceral and phrenic inputs (Chandler et al., 1999). In line with these findings, it was shown that the trigeminal subnucleus caudalis, located in the medullar dorsal horn and involved in the orofacial nociceptive transmission, receives extensive convergence inputs from cutaneous, muscular and visceral afferents (Sessle et al., 1986).

A neurophysiologic connection between cardiac vagal afferents and trigeminal and trigemino-thalamic neurons was also documented and a modulatory action of cardiac inputs on the trigeminal system was demonstrated (Bossut and Maixner, 1996). The excitatory effect of cardiac nociceptive afferent fibers on C1-C3 neurons that also receive somatic inputs from the craniofacial structures provides data for a potential neurophysiological mechanism that may explain referred pain to the face during myocardial ischemia (Chandler et al., 1996; Qin et al., 2001). More support for this hypothesis was given by Qin and coworkers, who showed that 89% of C1-C2 spinal neurons that respond to intrapericardial algogenic substances are also excited by mechanical stimulation of the craniofacial structures innervated by trigeminal afferent fibers (Qin et al., 2001).

The relative contribution of vagal and sympathetic afferent fibers for transmission of nociceptive input from the heart to C1-C2 neurons is controversial. However, experimental data from animal models indicates that both systems are involved and suggests that C1-C2 spinal neurons may act as an integrating center for cardiac nociceptive

input that travels in both vagal and sympathetic afferent fibers (Qin et al., 2001). Research data strongly suggests that cardiac vagal afferents specifically contribute to jaw and neck pain of cardiac origin because 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 (Chandler et al., 1996; Foreman, 2007). The hypothesis of a neural connection between cardiac vagal inputs and spinothalamic C1-C2 neurons (Fig. 1) is also supported by McNeill and coworkers, who found that approximately 6% of neurons from the nodose ganglion project fibers to the upper cervical spinal cord (McNeill et al., 1991). In addition to this data, other studies have found that transection of the vagus nerve eliminated the neural activity at C1-C2 neurons which was elicited by the injections of algesic substances in the pericardium (Qin et al., 2001; Foreman and Qin, 2009).

## Acute coronary syndrome: general considerations.

During the last decades the term "acute coronary syndrome" (ACS) has been taken to describe a variety of clinical signs and symptoms that are related to acute myocardial ischemia (Anderson et al., 2007), a condition of insufficient blood flow to the heart muscle as a consequence of a perfusion imbalance between myocardial oxygen supply and demand. Severe and/or prolonged myocardial ischemia can lead to myocardial infarction, with its associated cardiac cell death and release of biomarkers of myocardial necrosis, such as troponin I and troponin T, which can be detected by specific laboratory testing (Thygesen et al., 2007; Anderson et al., 2007).

The pathophysiology underlying ACS involves the narrowing or obstruction of a coronary artery, generally due to atherosclerotic plaque disease and thrombus formation. Atherosclerosis is a systemic disease involving arteries of medium and large diameter. Typical characteristics of this disease include thickening of the intima, lipid and cellular deposits surrounded by a capsule of connective tissue (plaque) and changes in the media and adventitia (for review see Davies, 2000; Corti et al., 2002). In the early stages of plaque formation the endothelium is usually not damaged, while in more advanced stages of the disease endothelial dysfunction and plaque capsular disruption may occur, promoting thrombus formation and coronary artery occlusion (Stary et al., 1995; Davies, 2000).

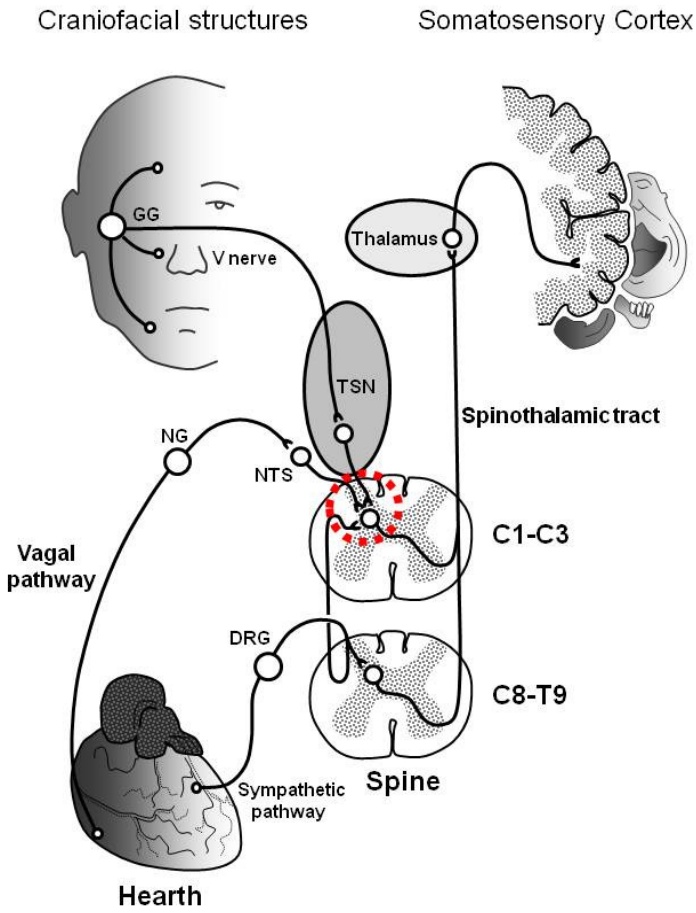


**Figure 1.** *Potential mechanism of craniofacial pain referred from the heart.* Schematic drawing based on data from experimental and clinical research, which illustrates the neurophysiological mechanisms for craniofacial pain of cardiac origin. Sympathetic, vagal and trigeminal inputs converge in 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.

This process of arterial occlusion (Fig. 2) and consequent reduced perfusion constitute the main pathology involved in myocardial ischemia.

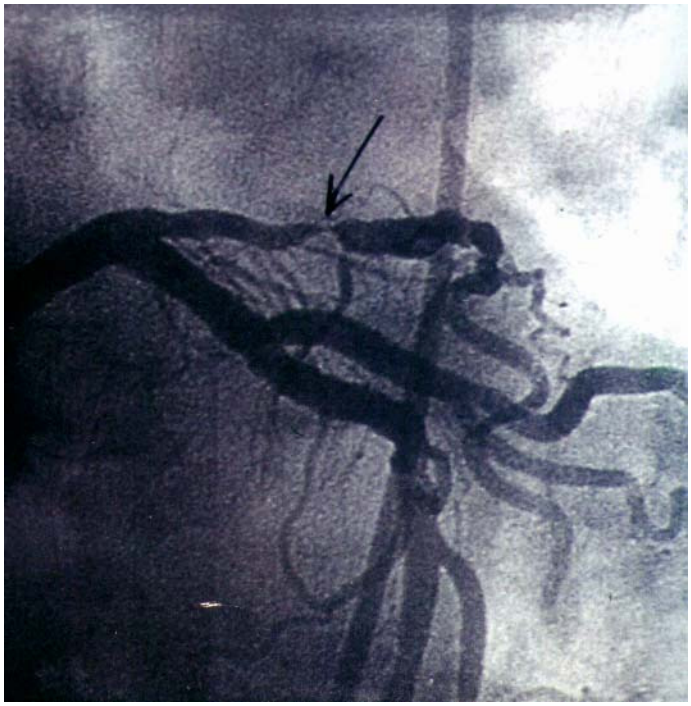

**Figure 2.** Angiogram depicting a severe occlusion in a coronary artery. Published in: Kreiner and Okeson, J Orofac Pain 1999;13:201-207. Reproduced with permission from Quintessence Publishing Co Inc, Chicago.

Based on its clinical presentation, electrocardiographic features and serum levels of cardiac biomarkers, two major ACS conditions can be differentiated: unstable angina and myocardial infarction (Cannon et al., 2001; Luepker et al., 2003; Fox et al., 2004). While in chronic stable angina the cardiac symptoms present in a pattern that tend to remain constant over time, unstable angina presents with new or changing symptoms in a crescendo pattern and can also occur at rest (Luepker et al., 2003). When myocardial infarction occurs several cardiac biomarkers may be detected, usually in combination with one or more of the following: symptoms of ischemia, ECG changes with development of

pathological Q waves, new ST-T changes and imaging evidence of new loss of viable myocardium or new wall motion abnormality (Thygesen et al., 2007).

## Clinical presentation of symptomatic acute myocardial infarction.

Understanding the clinical characteristics of an AMI is a key factor in prompt and accurate diagnosis. Guidelines for clinicians suggest assessment of the patient's pain, if present, by evaluating the symptom location, quality, intensity, and duration, with any aggravating, relieving and radiating factors being taken into account (Thygesen et al., 2007; Anderson et al., 2007). Typically, cardiac pain is described as being localized in the sternal region and left side of the chest but it can also radiate to the neck, either arm, the shoulders, the stomach and the jaws (Biagini et al., 1989; Eriksson et al., 1994). The general public, however, would generally only recognize pain in the middle of the chest as a symptom of an AMI (Zerwic, 1998). The presence and intensity of pain is variable but is not associated with disease severity; both symptomatic and asymptomatic episodes can present with similar cardiac hemodynamic changes (Chierchia et al., 1983).

Guidelines also recommend enquiring into many additional factors, even though the pain may be the predominant symptom. These factors include other symptoms such as breathlessness, palpitations, weakness, nausea, sweating and vertigo, as well as the patient's gender, age, history of ischemic heart disease and other cardiovascular risk factors. Prolonged pain (>20 minutes), worsening angina, arrhythmia and hypotension are considered to be high risk clinical features (Antman et al., 2004).

### *Influence of age and gender*

Age and gender influence the symptom presentation of an AMI. It has been shown that elderly patients complain of significantly less pain in the left arm, right arm, and neck than younger patients (Everts et al., 1996), while Then and coworkers (2001) found that the influence of age in symptom presentation was more significant in patients over the age of 75. There is increasing medical concern that women who experience an acute myocardial infarction tend to receive appropriate therapy less

often than men and have poorer outcomes (Cohen et al., 2005). Gender differences regarding symptom presentation during an AMI were reported by several studies, with women being less likely to report discomfort in the center of the chest (Kannel, 2002; King and McGuire, 2007) and more likely to report digestive symptoms, palpitations, nausea and unusual fatigue (DeVon et al., 2008). However, one study did not find gender differences when comparing typical and atypical symptoms during an AMI (Isaksson, 2008). A better understanding of possible differences in symptomatology between women and men during myocardial ischemia is important in order to avoid disparities in medical management between genders (D'Antono et al., 2006).

## *Myocardial infarction presenting without chest pain.*

Patients with acute myocardial infarction who present without chest pain are often misdiagnosed and are consequently less likely to receive appropriate therapy and have a higher risk of death (Uretsky et al., 1977; Fesmire and Wears, 1989; Canto et al., 2000; Dorsch et al, 2001; Brieger et al., 2004; Hirakawa et al., 2006; Zdzienicka et al., 2007). This risk of death could be three times higher than that of patients seeking care for chest pain during emergency department evaluation (Fesmire and Wears, 1989). Furthermore, these same patients, who never developed chest pain, had a risk of death eight times greater than that of patients whose chest pain resolved before they received hospital care.

The reported prevalence of AMI presentation without chest pain ranges between 8% and 30% (Herlitz et al., 1992; Brieger et al., 2004; Dorsch et al., 2001; Canto et al., 2000). This subgroup of patients has a significantly greater delay between the onset of symptoms and arrival at the hospital (Uretsky et al., 1977) and in consequence a higher mortality rate (Herlitz et al., 1992). It is highly probable that many individuals died before being admitted to the emergency room and thus were not included in the published research data, indicating that the reported prevalence is probably an underestimation.

Early recognition of this high-risk group should improve survival (Shlipak et al., 2000). However, only a few studies were conducted focusing on myocardial ischemia presenting without chest pain and several methodological limitations can be observed. Most of the large studies focusing on this issue are retrospective and include data from

regional (Dorsch et al., 2001), national (Canto et al., 2000) and international registries (Brieger et al., 2004). This type of study design necessarily means that the quality and accuracy of the analyzed data depends 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, e.g. by including subjects from clinical trials (Goldstein et al., 1995) or by including only AMI patients (Uretsky et al., 1977; Goldstein et al., 1995; Canto et al., 2000; Dorsch et al., 2001; Hirakawa et al., 2006).

## Craniofacial pain as the sole symptom of myocardial ischemia

Patients who experience craniofacial pain as the sole symptom of myocardial ischemia are likely to seek dental or oto-rhino-laryngological treatment and the possibility of misdiagnosis is high. Until the publication of our studies, the clinical link between craniofacial pain and myocardial ischemia was anecdotal and reported in the literature only as case reports (Tzukert et al., 1981; Batchelder et al., 1987; Penarocha et al., 1990; Takayanagi et al., 1990; Rothwel, 1993; Ishida et al., 1996; Grace et al., 1997; Kreiner and Okeson, 1999). Toothache, mandibular pain, ear pain and headache were the most common reported pain locations.

Misdiagnosis, mistreatment and delay in administration of appropriate therapy were common features in those reports. One typical case described anginal pain experienced in the mandible alone, which resulted in unnecessary dental treatment and a delay in appropriate management (Batchelder et al., 1987). This was a 71 year-old male who complained to his dentist of dental pain, which was initially diagnosed as odontogenic, secondary to pulp disease, in a mandibular first premolar. Endodontic treatment was performed but the pain did not resolve. The patient was then referred for a diagnostic consultation. An ECG showed myocardial ischemia and coronary angiography showed 90% occlusion of the left anterior descending coronary artery. Nitroglycerin medication took away the “dental” pain.

Headache and ear pain can also be correlated with acute coronary disease, while two fatal cases of angina pectoris were reported in patients who primarily complained of headache (Takayanagi et al., 1990; Rothwell, 1993; Grace et al., 1997).

## Prodromal angina and recurrent ischemia

Prodromal angina (also called pre-infarction angina) constitutes one or several acute myocardial ischemic episodes prior to an AMI, which can occur several hours, weeks or months before an AMI (McSweeney et al., 2003; Graham et al., 2008). Early prodromal warnings of an AMI are not well known either by the public or by clinicians. Patients reported that they had ignored these prodromal symptoms, whereas others sought medical assistance but the condition was minimized, misdiagnosed or ignored by clinicians (McSweeney et al., 2001; McSweeney et al., 2003).

Prodromal angina was shown to be a strong predictor of better survival and smaller infarct size (Bahr et al., 2000; Christenson et al., 2003). The physiological mechanisms underlying the protective role of prodromal angina is known as "ischemic preconditioning" and was shown in controlled experimental animal models to reduce the infarct size by 75%, when the myocardium is exposed to cycles of coronary artery occlusions followed by periods of reperfusion prior to an infarct (Murry et al., 1986). The biological mechanisms triggered by this cardioprotective phenomenon are complex and still not well understood. However, research data points to the involvement of several mediators including bradykinin, adenosine and opioids as well as signaling kinases and mitochondrial molecules of the myocardium (for review see Hausenloy and Yellon, 2009).

Although ischemic preconditioning is one of the most powerful and reproducible phenomena in cardioprotection, its induction is not routinely used in clinical practice (Kloner, 2009). However, this physiologic mechanism has important clinical and therapeutic implications and a recent randomized clinical trial has shown that ischemic preconditioning has a myocardial protective effect in patients who undergo cardiac surgery (Cheung et al., 2006). This study included children undergoing repair of congenital heart defects and performed remote ischemic preconditioning by inducing four 5-minute cycles of ischemia and reperfusion at the lower limb. Compared to the control group, the ischemic preconditioning patients had lower levels of troponin I postoperatively, indicating lower myocardial injury. It has previously been assumed that the window of protection of the preconditioning mechanism lasts only for a few days (Baxter et al., 1997)

but a recent clinical study suggests that it can last for weeks (Mladenovic et al., 2008).

Until now, the inclusion criteria for clinical research on prodromal angina have included chest pain/discomfort with or without other symptoms (Ishihara et al., 2003; Takusagawa et al., 1999; Bahr et al., 2000; Christenson et al., 2003; Papadopoulus et al., 2005; Jiménez et al., 2008; Maruhashi et al., 2010). Thus, the possibility of prodromal angina presenting as craniofacial pain alone has so far not been addressed.

If variation in the set of symptom characteristics of a medical condition is overlooked, this is likely to affect the results of decision-making models (Koffijberg et al., 2009). Most studies on variation in symptom presentation during cardiac ischemic episodes and AMI have been based on inter-individual comparisons. Only a few studies have focused on intra-individual variability and they have mainly been limited to ECG findings regarding the frequency and duration of transient ischemic episodes (Nabel et al., 1988), alterations of autonomic nervous activity during angina (Takusagawa et al., 1999) and the intra-individual variability in plasma levels of markers of cell damage (de Maat et al., 1996). Intra-individual variation in the presentation of atypical symptoms during recurrent acute ischemic episodes has not yet been investigated.

# OBJECTIVES

The overall aim of this thesis is to contribute to the clinical and diagnostic understanding of craniofacial pain of cardiac origin, with a special focus on craniofacial pain as the sole symptom of an AMI or a pre-infarction ischemic episode.

## The specific aims are:

a. To describe the prevalence and distribution of pain induced by myocardial ischemia (with or without an AMI) which is referred to the face, neck, head and mouth and to analyze possible age and gender differences (I).

b. To ascertain any differences in clinical presentation of referred craniofacial pain due to cardiac versus dental origin and to evaluate the diagnostic potential of the findings (II).

c. To identify the probability of pre-infarction angina presenting with craniofacial pain as the sole symptom and to analyze the intra-individual variations in pain characteristics and ECG findings in patients who experienced at least two cardiac ischemic episodes (III).

d. To evaluate any association between the absence of chest pain or the presence of craniofacial pain during myocardial ischemia and pain characteristics, risk factors, age, gender, and location of ischemia in the heart (IV).

# MATERIAL AND METHODS

## Study populations and diagnostic criteria.

### *Patients with referred pain of cardiac origin*

Patients with a verified episode of myocardial ischemia were derived from 404 subjects who were admitted with potential signs and/or symptoms of myocardial ischemia to three cardiology units in Montevideo, Uruguay: The Department of Cardiology, Hospital de Clínicas, the Instituto Nacional de Cirugía Cardíaca (INCC) and the Hospital Central de las Fuerzas Armadas. Patients were seen consecutively during recruitment periods that were spread over the year in order to avoid seasonal effects. Twenty patients could not be interviewed due to death or prompt dismissal for follow-up treatment elsewhere. The remaining 384 patients were examined and interviewed. Patients were excluded (n=58) when myocardial ischemia was not verified, craniofacial pain was from non-cardiac origin (e.g. dental pain, orofacial infections, muscle pain, TMJ pain, cancer pain, etc.), ischemia was asymptomatic, or the patients had severe heart failure, psychiatric disorders or confusion (Table 1).

| Reason for exclusion | n |
|---|---|
| Normal cardiologic examination. | 25 |
| Craniofacial pains from non-cardiac origin | 18 |
| Asymptomatic ischemia | 9 |
| Severe heart failure | 3 |
| Psychiatric disorders or confusion | 3 |
| Total | 58 |

**Table 1.** Reasons for exclusion of patients.

A total of 326 consecutive patients were included in the project, having met the criterion of having symptomatic myocardial ischemia, with or without an AMI. Of these, 176 patients experienced only one symptomatic episode of myocardial ischemia, while 150 patients experienced at least two episodes within five months of each other. In the latter group of 150 patients, the last two episodes of symptomatic myocardial ischemia were included in the intra-individual variability analysis[III]. An AMI was experienced by 120 patients (39 women and 81 men, mean age 63 years) and was classified as having an "abrupt onset" or "AMI with prodromal angina", according to previous definitions[III] (Bahr et al., 2000; Christenson et al., 2003). Seven patients had recurrent AMI but no prodromal symptoms and were not included in any AMI group. Table 2 presents data regarding the main subgroups, inclusion criteria, age and gender.

Myocardial ischemia, AMI and location of ECG changes were diagnosed by cardiologists according to the American College of Cardiology criteria (Cannon et al., 2001). Ischemia-related symptoms which had been experienced within five months prior to the occurrence of an AMI were regarded as prodromal[III,IV] (McSweeney et al., 2003; Graham et al., 2008).

| Paper | Patients (n) | Inclusion criteria | Mean age | Gender |
|---|---|---|---|---|
| I | 186 | Pain during cardiac ischemia | 64 | 76 F, 110 M |
| II | 115 | Craniofacial pain during cardiac ischemia | 64 | 56 F, 59 M |
| III | 81 | AMI with abrupt onset | 64 | 24 F, 57 M |
| | 32 | AMI with prodromal angina | 61 | 15 F, 24 M |
| IV | 326 | Pain during cardiac ischemia. | 64 | 134 F, 192 M |

**Table 2.** Study populations and main subgroups of cardiac patients included in each of papers I-IV. AMI: acute myocardial infarction.

### *Patients with referred craniofacial pain of dental origin*

Patients with referred craniofacial pain of dental origin were derived from a total of 400 patients (217 females, 183 males, age range 17 - 73 years) reporting to the dental emergency clinic at the University of Kentucky, College of Dentistry, USA (Falace et al., 1996) with complaint of posterior toothache. The inclusion criterion was posterior toothache clinically verified as being attributed to one tooth according to acknowledged criteria (Cailleteau, 1995). The study group (dental craniofacial pain group) comprised 359 patients (196 females, 163 males) with dental pain which was referred to the craniofacial region. Seventeen patients were unable to rank pain intensity and were excluded from the intensity analysis[II].

## Data collection

Demographic details on age, gender and pain characteristics (location, quality and intensity) were assessed in all patient groups. Cardiovascular conventional risk factors (hypertension, diabetes mellitus, smoking, family history of coronary artery disease, hypercholesterolemia and obesity), cardiac diagnosis and ECG findings were also assessed in the cardiac pain groups.

### *Pain intensity*

Pain intensity was marked for each reported location on a numerical rating scale ranging from 0 to10, which is validated for corresponding verbal descriptors (Borg, 1982), as follows: 0 “Nothing at all”, 1 “Very weak”, 2 “Weak”, 3 “Moderate”, 4 “Somewhat strong”, 5-6 “Strong”, 7-8-9 “Very strong”, 10 “Extremely strong”.

### *Pain quality*

Patients were asked to describe the quality of pain for each reported location using a list of pain descriptors from the McGill Pain Questionnaire (Melzack, 1975) which is psychometrically validated for both English and Spanish languages (Melzack, 1975; Lazaro et al., 2001). They were also asked to describe the pain in their own words using as many descriptors as necessary.

## *Pain location*

The patients were encouraged to describe in detail not only the main location of pain, but also any other locations of less intensity**.** Painful areas were marked on a full-body schematic drawing including specific views of the intra-oral, head, and neck areas (Fig. 3).

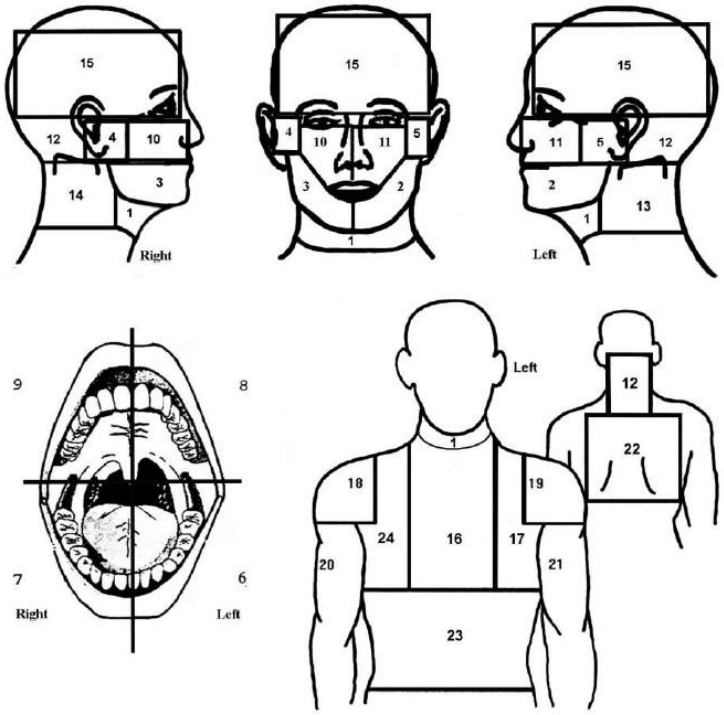


**Figure 3.** Schematic drawing of the body and the craniofacial structures subdivided into different areas. Published in: Kreiner et al, J Am Dent Assoc 2007;138:74-79. Reproduced with permission from the American Dental Association.

## *Location of myocardial ischemia.*

The locations of ECG findings were categorized as anterior (leads V1 to V4), inferior (leads II, III, aVF) and lateral (leads I, aVL, V5 to V6) according to accepted criteria (Cannon et al., 2001).

## Statistical methods

In order to determine normality, graphic methods (histograms and box plots) and statistical tests (Kolmogorov-Smirnov) were used. Because the samples were not normally distributed, non-parametric methods were used to analyze the data. Statistical significance was determined at a $p < 0.05$ significance level.

Chi-square tests were used to assess differences in symptom distribution between groups. The Mann Whitney U (Wilcoxon rank-sum) test was used to assess differences between two independent samples (e.g. pain intensity, mean age between groups)[I-IV]. The Wilcoxon signed-rank test was used to analyze intra-individual variations of pain intensity[II,III].

A discriminative analysis (sensitivity, specificity, etc) and ROC curves were performed in order to evaluate the diagnostic potential of the findings regarding pain quality and intensity[II]. The McNemar's test was used to assess the significance of the differences between intra-individual episodes when the variable was dichotomous (e.g. AMI) and the Marginal Homogeneity test was used when the variable was multinomial (e.g. quality of pain, site of ischemia)[III].

A multivariate logistic regression model was used to analyze possible associations between the presence of prodromes, absence of chest pain, presence of craniofacial pain (dependent variables) and age, gender, cardiovascular risk factors and location of ischemia. Two age subgroups (<65 and >65) were established when controlling for covariates in the logistic regression models[III-IV].

Sample size calculations were performed with the Kelsey and Fleiss formula, assuming a power of 80% and accepting a statistical difference at the 5% level.

The SPSS software (Version 9, Chicago, IL, USA) and the "R" software with the "epiR", "coin" and "stats" packages (Hothorn et al., 2006; Hothorn et al., 2008) were used to perform the statistical analyses.

## Ethics approval

The Ethics Committees at the Universidad de la República, the Hospital Central de las Fuerzas Armadas, Uruguay, and the University of Kentucky, USA, approved the relevant sections of the study protocol. Informed consent was obtained from each patient included in the study.

# RESULTS

## Prevalence of craniofacial pain in myocardial ischemia, analysed for age and gender differences.

Pain in the craniofacial region was experienced by 71/186 patients (38%) during myocardial ischemia[I]. Sixty patients (32%) reported referred craniofacial pain with concomitant pain in typical anginal regions such as chest, shoulder, back and/or arms, while 11 patients (6%) experienced craniofacial pain alone during myocardial ischemia (Fig. 4). The ischemic event was associated with an AMI in 74 patients (40%). During the AMI, 27 of these patients (36%) experienced craniofacial pain, three of whom were men (4%) with no other concomitant symptoms (Fig. 4). The observed frequencies remained largely unchanged when the material was extended to 326 patients[IV]. Twelve percent (n=38) of patients did not experience chest pain during the myocardial ischemia episode. The corresponding figure during an AMI was 15% (n=18)[IV].

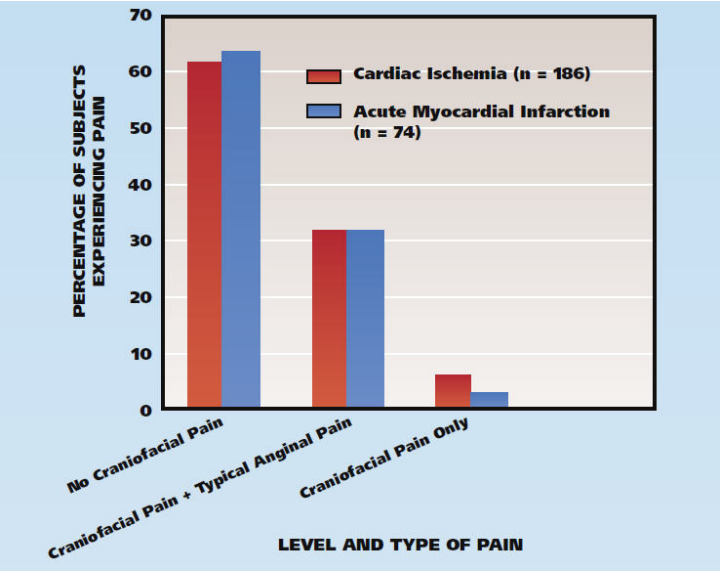


**Figure 4.** Prevalence of referred craniofacial pain during myocardial ischemia and acute myocardial infarction. Published in: Kreiner et al, J Am Dent Assoc 2007;138:74-79. Reproduced with permission from the American Dental Association.

Pain in the craniofacial areas constituted the sole prodromal symptom of an AMI in 5% (n=6) of patients (Table 3). Prodromal craniofacial pain in combination with typical anginal locations (chest, arms, shoulders, etc) was experienced by another 12% (n=14) of the AMI patients (n=120)[III].

| Myocardial ischemia with and without AMI | AMI | Prodromal angina |
|---|---|---|
| 6% | 4% | 5% |

**Table 3.** Overall prevalence of craniofacial pain as the sole symptom of myocardial ischemia during different conditions. AMI: Acute myocardial infarction.

Craniofacial pain of cardiac origin was more frequently reported in women[I] (p=0.031). When comparing pain characteristics between craniofacial pain of cardiac versus dental origin[II] there was no gender difference regarding pain quality or intensity in either group. After most data of the dental craniofacial pain group was statistically analyzed, the corresponding questionnaires with demographic data were destroyed by flooding of a storage room and the mean age calculations lost. However, we know that the mean age of this group was approximately 35 years.

## Pain location

Figure 5 shows the distribution of craniofacial areas affected by pain induced by myocardial ischemia in 71 patients[I]. The areas most frequently affected were the upper part of the throat (n = 58, 82%) and the left mandible (n = 32, 45%), followed by the right mandible (n = 29, 40%) and the left TMJ/ear region (n = 13, 18%). The maxilla and the posterior neck were the sites least frequently affected by referred cardiac pain. Toothache occurred in three patients, affecting mandibular teeth bilaterally in two patients and the left maxillary teeth in the third. Pain in the TMJ/ear was bilateral in 11 patients and unilateral (left) in two. The ratio for bilateral referral pattern of pain to the craniofacial structures versus unilateral was 6:1. The ratio for

bilateral versus unilateral referred pain to the arms was 1:1. When arm pain was unilateral, it referred to the left arm in 22 patients and to the right arm in four[I].

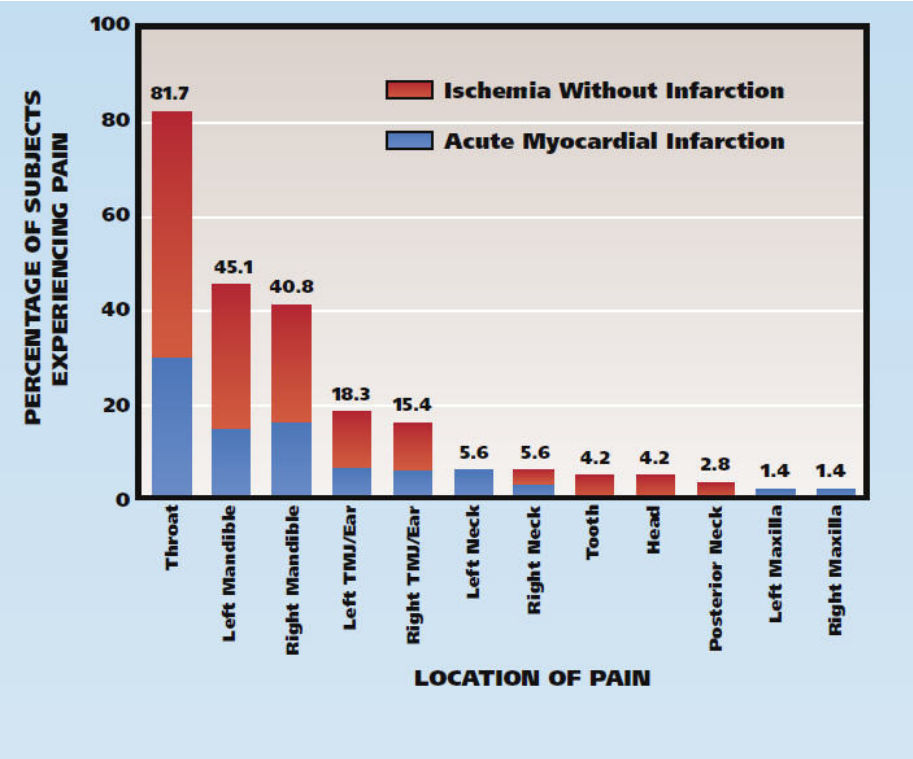


**Figure 5**. Distribution of referred craniofacial pain during myocardial ischemia and myocardial infarction (n=71). TMJ: Temporomandibular joint. Published in: Kreiner et al, J Am Dent Assoc 2007;138:74-79. Reproduced with permission from the American Dental Association.

During pre-infarction (prodromal) ischemic events, the reported craniofacial pain locations were the same. All 6 patients with craniofacial pain as the sole prodromal symptom of an AMI reported a difference in pain location between episodes. During the AMI all these patients again reported craniofacial pain but five of them also developed chest pain and one had back pain in addition to the craniofacial pain. Only one of their clinicians had an early suspicion of a possible cardiac source of the prodromal facial pain[III].

In the absence of chest pain, the most prevalent pain location was the craniofacial area. Table 4 shows the distribution of pain locations for this subgroup of patients[IV].

**Patients Without Chest Pain**

| Location of Pain | Prodromal Angina n= 9 | | Ischemia with AMI n=18 | | Ischemia without AMI n=20 | |
|---|---|---|---|---|---|---|
| | % | with 95% CI | % | with 95% CI | % | with 95% CI |
| Craniofacial | 67 | (0.29-0.92) | 44 | (0.21-0.69) | 80 | (0.56-0.94) |
| Left shoulder | 33 | (0.07-0.70) | 16 | (0.03-0.41) | 10 | (0.01-0.31) |
| Stomach | 22 | (0.02-0.60) | 33 | ( 0.13-0.59) | 10 | (0.01-0.31) |
| Left arm | 11 | (0.00-0.48) | 16 | (0.03-0.41) | 20 | (0.05-0.43) |
| Back | 11 | (0.00-0.48) | 11 | (0.01-0.34) | 10 | (0.01-0.31) |
| Right shoulder/arm | 0 | | 16 | (0.03-0.41) | 10 | (0.01-0.31) |

**Table 4.** Distribution of pain locations in patients who did not experience chest pain during myocardial ischemia. CI: Confidence interval. AMI: Acute myocardial infarction.

## Pain quality.

Four quality descriptors (aching, burning, pressure and throbbing) were found to have high validity for guiding to a differential diagnosis between craniofacial pain of cardiac versus dental origin[II] (Table 5). When craniofacial pain was the sole symptom of myocardial ischemia the descriptors "pressure" and/or "burning" were used by all except one patient in this group, with "pressure" being more frequently reported by those patients without acute myocardial infarction[II] ($p=0.017$). These same quality descriptors were used by all patients who reported craniofacial pain as the sole symptom of a pre-infarction episode[III]. When patients had more than one ischemic episode, the combination of pain quality descriptors between episodes generally changed significantly ($p=0.01$) but the quality descriptors "pressure" and "burning" remained the same between episodes[III].

The descriptor "sharp" was used by both groups with a preponderance in the dental group ($p<0.001$). Overall distribution of pain quality descriptors differed between groups[II] (Fig. 6).

| Descriptor | Positive Dental CFPG | Positive Cardiac CFPG | Specificity with 95% CI | Sensitivity with 95% CI |
|---|---|---|---|---|
| **Aching** | **n=215** | **n=5** | **0.96(0.91, 0.98)** | **0.6(0.55, 0.65)** |
| **Burning** | **n=22** | **n=54** | **0.94(0.91, 0.96)** | **0.47(0.38, 0.56)** |
| **Pressure** | **n=0** | **n=78** | **1(0.99, 1)** | **0.68(0.59, 0.76)** |
| **Throbbing** | **n=211** | **n=1** | **0.99(0.96, 1)** | **0.59(0.54, 0.64)** |

**Table 5.** Discriminative analysis for those quality descriptors with high clinical relevance. CI: Confidence interval. CFPG: Craniofacial pain group. Published in: Kreiner et al, J Dent Res 2010;89:965-969. Reproduced with permission from the Journal of Dental Research.

When patients with myocardial ischemia felt pain in multiple areas of the body, the pain was consistently (100%) described to be of the same quality between intra-individual sites. There was no statistically significant difference in gender distribution between the dental and cardiac craniofacial pain groups (p=0.53).

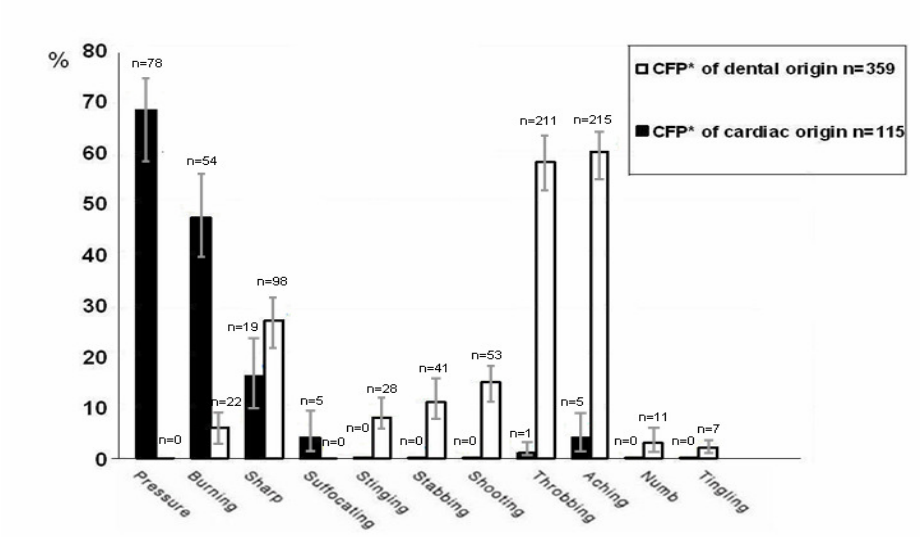


**Figure 6**. Distribution of quality descriptors for referred craniofacial pain of cardiac and dental origins[11]. Error bars represent 95% confidence intervals. CFP= craniofacial pain. Published in: Kreiner et al, J Dent Res 2010;89:965-969. Reproduced with permission from the Journal of Dental Research.

## Pain intensity

Similarly, there was no gender difference regarding pain intensity. Pain intensity was higher in the dental than in the cardiac craniofacial pain group (p=0.043)[II]. ROC curve analysis for intensity is shown in Figure 7. Most patients in both groups (>77%) rated their pain intensity as strong or worse. An intra-individual comparison within the cardiac craniofacial pain group revealed pain in the craniofacial regions to be significantly less intense than pain in typical anginal areas (p=0.001) with no difference by age or gender[II]. In those patients who experienced an AMI with a pre-infarction episode, pain intensity was higher during the AMI (p< 0.001)[III].

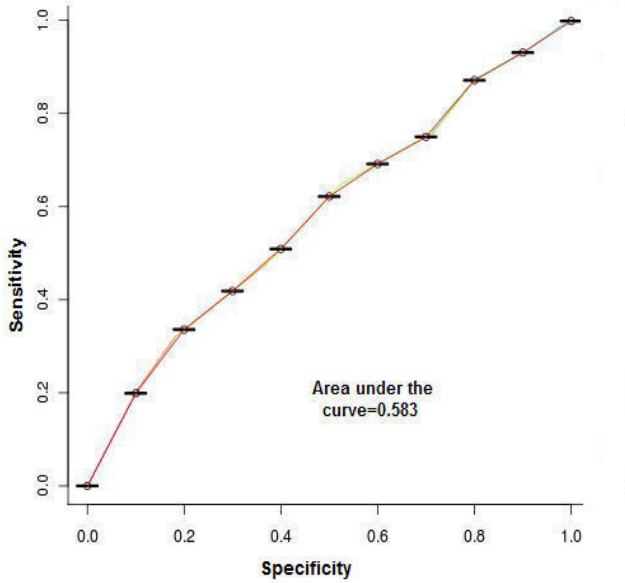


**Figure 7**. ROC curve analysis for pain intensity of cardiac vs. dental origin.

Five out of the six patients with craniofacial pain as the sole prodromal symptom of an AMI reported that exercise aggravated the intensity of symptoms and that rest alleviated the pain[III].

## Location of ischemia

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=<0.001) (Table 6), even without an AMI (p=0.005)[IV]. Of the 150 patients who experienced at least two episodes of myocardial ischemia, four with prodromal angina had not sought medical care for their prodromal symptoms and were discarded from the intra-individual variation analysis of the location of ECG changes[III]. The location of ischemia did not vary significantly between episodes (p=0.32)[III]. No association was found between the location of ischemia and absence of chest pain during myocardial ischemia (Table 6)[IV].

## Risk factors

The conventional risk factors found to be associated with craniofacial pain of cardiac origin were diabetes (p=0.014) and family history of cardiovascular disease (p=0.032) (Table 6)[IV]. Patients in the prodromal angina group were more likely to be obese (p=0.026) and also tended to have a family history of cardiovascular disease (p=0.05)[III]. No association was found between risk factors and absence of chest pain during myocardial ischemia[IV].

| | Myocardial ischemia n=326 | | | | 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% | Without CFP n=200, 61% | p value | Odds ratio (95% CI) |
| **Hypertension** | n= 203, 70 % | n=24, 63% | 0.456 | 0.75(0.36-1.57) | n=86, 68% | n=141, 70% | 0.372 | 0.78(0.46-1.33) |
| **Diabetes mellitus** | n= 87, 30 % | n=8, 21 % | 0.314 | 0.64(0.27-1.51) | n=47, 37% | n=48, 24% | **0.014** | 1.93(1.18-3.15) |
| **Smoking** | n= 154, 53 % | n=26, 68 % | 0.246 | 1.57(0.73-3.35) | n=64, 51% | n=116, 58% | 0.361 | 0.79(0.48-1.30) |
| **Family history of CAD** | n= 137, 47 % | n=16, 42 % | 0.673 | 0.85(0.42-1.74) | n=69, 55% | n=84, 42% | **0.032** | 1.70(1.03-2.79) |
| **Hypercholesterolemia** | n= 183, 63 % | n=26, 68 % | 0.329 | 1.45(0.68-3.11) | n=88, 70% | n=121, 61% | 0.215 | 1.37(0.83-2.27) |
| **Obesity** | n= 108, 37 % | n=13, 34 % | 0.865 | 0.93(0.45-1.95) | n=42, 33% | n=79, 40% | 0.116 | 0.67(0.41-1.10) |
| **Anterior Ischemia*** | n= 176, 61 % | n=17, 45 % | 0.331 | 0.62(0.24-1.61) | n=69, 55% | n=124, 62% | 0.666 | 1.13(0.63-2.03) |
| **Inferior ischemia*** | n= 113, 39 % | n=18, 47 % | 0.918 | 1.04(0.41-2.64) | n=66, 52% | n=65, 33 % | **<0.001** | 2.40(1.36-4.24) |
| **Lateral ischemia*** | n= 93, 32 % | n=14, 37 % | 0.559 | 1.28(0.55-2.97) | n=36, 29% | n=71, 36 % | 0.449 | 0.81(0.48-1.37) |

**Table 6**. Associations between groups and the analyzed covariates. CFP: craniofacial pain. CAD: coronary artery disease. CI: Confidence interval. * Location alone or in combination with other location.

# DISCUSSION

Most causes of referred craniofacial pain (e.g. dental, musculo-skeletal, sinusal, etc.) are widely described in the literature and are familiar to clinicians. However, the clinical characteristics of dental and facial referred pain of cardiac origin have not so far been well investigated or compared with pain of dental origin. Because there is a high risk of missed diagnosis when craniofacial pain presents as the sole symptom of myocardial ischemia, with consequent risk of fatal AMI, the results of this study should provide clinicians with new data that may be helpful for establishing an appropriate and prompt differential diagnosis.

## Epidemiological considerations

We found that craniofacial pain can be the sole symptom of an AMI in 4% of patients. Application of this percentage to the number of acute coronary heart disease patients in the US (Lloyd-Jones et al., 2009), indicates that more than 28,000 patients per year might experience craniofacial pain as the sole symptom of an AMI. The corresponding number for the UK would be 6,800 (Allender et al., 2007) and for Sweden 750 (Stenestrand and Wallentin, 2007).

Craniofacial pain as the sole symptom of myocardial ischemia and AMI has been overlooked as a research topic by epidemiological cardiovascular research. Several methodological problems may have played a role in this. For example, several studies that assessed location and characteristics of cardiac pain have excluded patients without chest pain (Cunningham et al., 1989; Eriksson et al., 1994; Kudenchuk et al., 1996; Goldberg et al., 2000). Furthermore, the questionnaire which has most commonly been used to assess cardiac pain in epidemiological studies for several decades, is the Rose Angina Questionnaire (Rose, 1962; Lawlor et al., 2003), which does not include the craniofacial structures in its schematic chart (Fig. 8). Patients included in many clinical research studies have therefore not had the opportunity to report in detail any craniofacial pain of cardiac origin. Furthermore, before the year 2000, researchers commonly used the 1979 WHO criteria in their diagnosis of AMI (For review see Chen et al 2005). These criteria may have excluded a considerable number of patients with atypical symptoms. In addition, most of the large scale epidemiological studies regarding symptom

presentation during myocardial ischemia and AMI utilized a retrospective design, by reviewing medical records and large registries. Retrospective research based on reviews of medical records has been widely used in clinical research for many decades but suffers from several limitations, such as incomplete or missing records, differences in accuracy of recording between physicians or difficulties in verifying the accuracy of the data. These limitations can introduce misclassification and confounding errors.

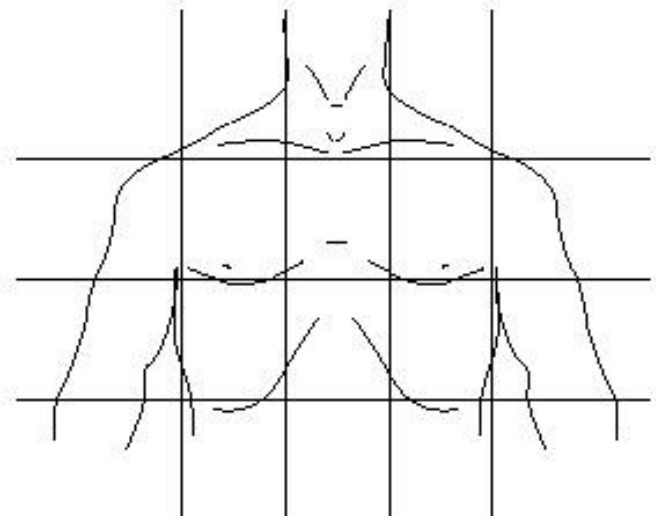

**Figure 8.** Rose angina diagram, commonly used in clinical research during decades.

Because public and clinical recognition of craniofacial pain as the sole symptom of myocardial ischemia is low (Then et al., 2001; Greenlund et al., 2004), patients with atypical symptoms run an increased risk for misdiagnosis and death (McCarthy et al., 1993; Pope et al., 2000). One case report showed that cardiac pain referred to the teeth resulted in misdirected dental treatment to a tooth and delay of appropriate medical care (Batchelder et al 1987). It is also highly probable that many individuals may have died prior to admission to hospital. Consequently, the reported prevalence of craniofacial pain as the sole symptom of myocardial ischemia and AMI found in our prospective study is probably underestimated.

### *Myocardial ischemia without chest pain*

There is a growing awareness that a considerable number of patients develop an AMI without suffering any chest pain (Fesmire and Wears, 1987; Herlitz et al., 1992; Canto et al., 2000; Hirakawa et al., 2006; Zdzienicka, 2007)). In our data, the prevalence of AMI presentation without chest pain was 15%[IV]. It is noteworthy that in previous studies, this prevalence varied between 8% and 30% (Herlitz et al., 1992; Canto et al., 2000; Dorsch et al., 2001; Brieger et al., 2004). Despite the methodological problems already discussed, the lack of homogeneity between definitions of typical and atypical pain and between chest pain group definitions during an AMI makes study comparison difficult and may explain the large differences between their results. In one report the chest pain group inclusion criterion was that the *"predominant"* presenting symptoms should include chest pain (Brieger et al 2004), meaning that the non-chest pain group may have had chest symptoms which were not "predominant". In another study (Canto et al., 2000) the chest pain group inclusion criterion was ¨….. *any symptom of chest discomfort, sensation or pressure,* ***or*** *arm, neck,* ***or*** *jaw pain..*¨, suggesting that patients with neck or jaw pain alone would have been included in the chest pain group, making the results difficult to interpret. Furthermore, no studies have been conducted to explore the possibility of pre-infarction angina presenting without chest symptoms. Our present studies revealed that in the absence of chest pain, the craniofacial structures were the main locations of pain during myocardial ischemia[I,IV], regardless of whether the patient was suffering an AMI or pre-infarction angina[IV].

## Bias control

Cardiac patients were recruited using a consecutive sampling method and in three different Coronary Units in order to guarantee the study material to be highly representative. In the Uruguayan Medical System, patients with suspected myocardial ischemia, who may come from any economic, social or cultural grouping, are always referred to these units for cardiologic evaluation. The referral is made by an emergency physician who performs preliminary tests (including ECGs) at the patient's home. This primary specialized screening explains the high percentage of patients with confirmed myocardial ischemia from those admitted to the coronary unit. Furthermore, we

recruited patients during all four seasons in order to minimize any possible confounding seasonal factors. Taking into account the research questions and the characteristics of the country's medical system, the sampling method that we used in this study is believed to be the most appropriate, allowing the sample to be highly representative of the general population who seek medical evaluation during a cardiac ischemic episode.

Patients with dental pain were recruited at a large dental emergency department in Lexington, Kentucky, USA[II]. This population is representative of patients with acute pain of dental origin who seek dental care. Furthermore, the results from this group of patients regarding dental pain quality are in line with the results of previous experimental studies (Ahlquist and Franzén, 1994; Ikeda and Suda, 2003).

Hence, the two patient groups in which craniofacial cardiac and dental pain were compared were recruited in cities from different countries: Montevideo, Uruguay (South America) and Lexington (USA) respectively[II]. Because the McGill questionnaire is validated for both English and Spanish and the gender distribution was similar between groups, the highly significant differences in pain quality reported for craniofacial pain of cardiac versus dental origin should not be biased.

In summary, considerable effort was made to ensure that this sample was an accurate representation of the general population and that the sampling method was the most appropriate to address the research questions.

## Prevalence, pain location and age, gender and risk factor differences

The typical presentation of cardiac pain is reported to be in the center and left side of the chest, often radiating to the arms and to the neck (Eriksson et al., 1994; Everts et al., 1996; Philpott et al., 2001). However, the results of our prospective study now broaden the diagnostic spectrum of common symptoms by demonstrating that craniofacial pain can be expected in approximately 40 percent of patients during a cardiac ischemic episode and is the sole symptom of myocardial ischemia in 6% of patients[I,IV]. The relative distribution for patients with an AMI was similar.

The most common site of craniofacial pain was the throat, followed by the mandible, the TMJs, the ears, the neck, and the teeth. These same regions are also typical for referred pain of odontogenic origin (Falace et al., 1996), although it has been observed that referred pain of odontogenic origin rarely crosses the midline (Falace et al., 1996), as opposed to craniofacial pain induced by myocardial ischemia, which, as revealed in this study, is mostly bilateral[I]. In contrast with craniofacial pain of cardiac origin, arm pain occurred bilaterally in only 50% of the cardiac patients. The complexity of the central processing of cardiac pain at different levels may explain these clinical differences (Foreman et al., 1999).

The results of our present studies indicate that referred pain felt in the mandible can be expected by one in six patients with myocardial ischemia[I,IV], while pain in the TMJ and ear region can be expected by one in 14 patients. The prevalence of toothache and headache was lower. Even though pain in the ear, TMJ or head had previously been associated with myocardial ischemia (Rothwell et al., 1993; Takayanagi et al., 1990; Philpott et al., 2001), pain in the craniofacial areas still constitutes a differential diagnostic challenge because of lack of awareness of the link to myocardial ischemia. A fatal outcome has been reported in patients with anginal headache as the sole symptom of myocardial ischemia (Takayanagi et al., 1990).

Age also differs between the cardiac and dental groups. Myocardial ischemia is diagnosed primarily in middle-aged and elderly patients while dental pain frequently occurs in younger adults and adolescents (Pau et al., 2007; Teoh et al., 2007; Bastos et al., 2008). The age range of our patient samples is in accordance with that of these earlier studies. It is reasonable to assume that the missing age data in the dental craniofacial pain group would have little impact on the results of this study, because age does not influence the quality of dental pain (Ikeda and Suda, 2003).

During the last decade, an increasing awareness has evolved regarding possible gender differences in presentation of symptoms induced by myocardial ischemia (Chen et al., 2005), together with treatment disparities between genders (Cohen et al., 2005). Some reports have found that women more often than men present with atypical symptoms (Philpott et al., 2001; Patel et al., 2004; Chen et al., 2005) while others did not found

significant differences (Isaksson et al., 2008). Methodological differences between studies regarding "atypical symptom" definition make results difficult to compare. In our present study we found a significant female predisposition to craniofacial pain of cardiac origin[I, IV].

## Craniofacial pain of cardiac versus dental origin

### *Quality*

The quality of pain referred to the same craniofacial regions was found to differ significantly between pain of cardiac and dental origins but with no difference between genders. The quality descriptors with the strongest statistical association with craniofacial pain of cardiac origin were "pressure" and "burning". "Pressure" was used by two thirds of patients in the cardiac craniofacial pain group but none in the dental craniofacial pain group. The absence of pressure-like pain in the dental craniofacial pain group is consistent with the results of experimentally induced dental pain (Ahlquist and Franzén, 1994; Ikeda and Suda, 2003). The use of the descriptor "suffocating" indicated a cardiac origin because only patients in the cardiac craniofacial pain group used it, but the limited sample size using "suffocating" to describe their pain yielded a power slightly below 80%.

The pain descriptors pointing to a dental origin were "throbbing" and "aching", and were used alone or in combination by almost two thirds of patients in the dental craniofacial pain group. Only one patient in the cardiac craniofacial pain group used the descriptor "throbbing". However, it seems that the perception of the quality of pain of cardiac origin can vary with different physiological and experimental conditions. Hence, "throbbing" and "numbness" in the head and neck have been reported by 15% of patients who experienced chest pain associated with myocardial ischemia during an exercise stress testing (D'Antono et al., 2006). It seems likely that the experimental setting of exercise stress testing may precipitate a neurovascular throbbing component as well as a numb sensation in the craniofacial structures that are not usually reported by patients during non-experimental conditions. This hypothesis of differential perception of cardiac pain during different conditions is given further support by the finding that women reported chest pain more often than men during daily activities but not during exercise (Sheps et al., 2001).

In summary, we found that the pain quality descriptors “pressure” and “burning” had a high diagnostic specificity for craniofacial pain of cardiac origin, while “throbbing” and “aching” suggested craniofacial pain of dental origin. Awareness of this data by clinicians should improve early diagnosis and survival.

### *Intensity*

Pain intensity was significantly higher in patients with craniofacial pain of dental origin but the ROC curve analysis showed that intensity is not an accurate means of differentiating between pain of cardiac versus dental origin. Since almost 80% of patients with craniofacial pain as the sole manifestation of myocardial ischemia described their pain as strong or worse, it can be assumed that many of these patients would seek treatment with a dentist or a general physician rather than cardiologic treatment.

While pain quality was consistent between different intra-individual locations, the pain intensity was significantly more intense adjacent to the cardiac source. The mechanisms underlying these differences in quality and intensity perception patterns are probably related to the complexity of the brain processing of cardiac pain. The secondary somatosensory (SII) cortex and the posterior insula cortex are involved in the intensity encoding of visceral pain and many bilateral networks of cortical structures participate in the processing of other pain characteristics (Dunckley et al., 2005). Furthermore, the convergence of visceral and somatic inputs onto common circuits in the central nervous system, including the trigeminal nucleus (Sessle et al., 1986; McMahon, 1997; Chandler et al., 1999) and the central sensitization phenomenon (Giamberardino et al., 1997; Laird et al., 2001) may explain, in part, the clinical findings of this study.

## Craniofacial pain as a prodromal symptom of an AMI

Ischemic preconditioning through pre-infarction angina has been shown to protect the myocardium, slow the process of cell death, reduce the infarct size, and improve patient prognosis (Murry et al., 1986; Kavianipour et al., 2003; Papadopoulos et al., 2005). Studies of pre-infarction angina and its protective role are largely limited to patients with chest

pain symptoms (Ishihara et al., 2003; Takusagawa et al., 1999; Bahr et al., 2000; Christenson et al., 2003; Papadopoulus et al., 2005; Jimenez, 2008) and have not considered prodromal craniofacial pain. Our study revealed that one in 20 AMI patients reported pain in the craniofacial structures as the sole prodromal symptom[III]. Considering that patients without chest pain during an AMI run a greater risk of death (Fesmire and Wears, 1989; Canto et al., 2000) and some of them may never reach the emergency room, it is highly plausible that our findings constitute an underestimation. It was also observed that patients with craniofacial pain as the sole pre-infarction alert consistently developed additional typical anginal symptoms during the AMI[III]. It may be that the pathological changes occurring during the AMI episode released several chemical mediators and activated more nerve afferent fibers, inducing changes in the pain pattern.

It is generally perceived among clinicians that atypical presentation of an AMI is a well-known problem but actual awareness appears low. One study (Then et al., 2001) found that 90% of nurses and 100% of physicians from an Emergency Care Unit in North America stated that they had experience with atypical presentations of an AMI but during the interview, pain in the craniofacial region was not cited by physicians or nurses as a symptom that would point to an AMI. In line with these findings, neither the patients with craniofacial pain as the sole prodromal symptom nor their clinicians recognized the cardiac origin of the pain in five out of six patients included in our study[III]. These findings point to the need for educational initiatives for both the general public and clinicians regarding this prodromal presentation.

We found that the quality descriptors “pressure” and “burning” were the main descriptors used by patients during pre-infarction craniofacial symptoms. These findings are in line with our results regarding quality of cardiac pain during an AMI[II]. The clinical information regarding pain quality, aggravation by exercise and pain relief during rest should alert the clinician regarding the possibility of an AMI prodromal condition.

Prodromal angina pectoris is a strong predictor of a smaller size infarct and lower mortality (Christenson et al., 2003), the 1-year lower mortality being more significant in women (Graham et al., 2008). Similarly,

a meta-analysis showed that the occurrence of prodromal angina in the 24 hours before the onset of an AMI was associated with a reduction of in-hospital mortality of 39% (Iglesias et al., 2005). This data clearly suggests that the craniofacial prodromal symptoms found in our study[III] constitute important clinical information. The explanation for the low recognition of this atypical symptom presentation is most likely that research on prodromal AMI symptoms has to date focused only on patients with chest pain as an inclusion criterion, regardless of other symptoms.

Previous studies reported that prodromal AMI symptoms were associated with the presence of certain risk factors, such as hypertension (Bahr et al., 2000; Graham et al., 2008). We performed an analysis of several risk factors and found only obesity[III] to be associated with the presence of prodromal symptoms.

## Location of ischemia in the heart and craniofacial pain

The occurrence of craniofacial pain was statistically associated with an inferior location of the myocardial ischemia[IV]. This finding lends support to a previously reported association between an inferior ischemic location and neck and jaw pain in patients with an AMI (Culić et al., 2001). Although Culić and coworkers only investigated patients with an AMI, our study found the same association in patients with myocardial ischemia without an AMI.

This clinical finding is in line with experimental research data suggesting that cardiac vagal afferents contribute to jaw and neck pain of cardiac origin. During experimental electrical stimulation of sympathetic and vagal afferent fibers, the spinothalamic tract neurons in C1-C2 related to somatic fields in the jaws and the neck were particularly responsive to vagal afferents (Chandler et al., 1996; Foreman, 2007). Further support for this hypothesis is given by data from surgical interventions, showing that even if sympathetic afferents play a major role in contributing to the pain generated during angina pectoris, vagal involvement is strongly implicated in conducting inputs from the inferior-posterior surface of the heart (Meller and Gebhart, 1992; Chandler et al., 1996).

Our hypothesis, that there is a 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 (Ansari et al., 2007), which is used to treat intractable depression and some types of refractory epilepsy. One case report described a patient who developed left-sided toothache after the implantation of a VNS (Myers, 2008), with episodes of pain which were intermittent and coincided with the duration of the VNS stimulus (30 seconds every 5 minutes). Other case reports have also described toothache and facial pain as a side effect of VNS in previously asymptomatic patients (Shih et al., 2003; Carius and Schultze, 2005).

## Correlations between risk factors and craniofacial pain

Diabetes has been associated with atherosclerotic disease (For review see Yang et al., 2010) and is statistically associated with higher mortality and atypical symptom presentation in ischemic heart disease; these include pain location and silent ischemia, mainly in patients younger than 70 years old (Donahoe et al., 2007; Hwang et al., 2009). It was estimated that younger adults with diabetes run a 2.5 fold higher risk of experiencing atypical symptoms during an acute coronary event compared with younger adults without diabetes (Hwang et al., 2009). However, a possible association between diabetes mellitus and craniofacial symptoms during myocardial ischemia has not previously been documented. We now show a statistically significant association between the presence of craniofacial pain during a cardiac ischemic episode in diabetics[IV].

## Clinical implications

Early recognition of an AMI and prompt therapy can play a critical life-saving role. The results of the present study could help clinicians make an accurate and prompt differential diagnosis when craniofacial pain is the sole symptom of myocardial ischemia.

One of the most common diagnostic tests performed by dentists and physicians in order to identify whether pain is referred is to inject local anesthetics. Local anesthesia injected in the site of referred pain would not affect the pain intensity but local anesthesia injected in the real source would eliminate the pain, guiding the clinician to an

accurate diagnosis and treatment. While this approach is appropriate in most craniofacial conditions, referred pain of cardiac origin is probably the only exception to this clinical protocol. Most local anesthetics used by clinicians are combined with vasoconstrictor drugs, which have important pharmacological effects on the cardiovascular system; injecting a local anesthetic into a patient who is experiencing facial pain due to coronary occlusion might aggravate the condition and put his or her life at risk.

## CONCLUSIONS

To our knowledge, this study is the first to report and analyze craniofacial pain as the sole symptom of myocardial ischemia (6%) and pre-infarction angina (5%). The prevalence found in this study points to the possibility of the potentially fatal misdiagnosis of many thousands of patients per year.

In order to initiate prompt and appropriate treatment, dental and medical clinicians, as well as the general public, should be aware of those clinical characteristics of craniofacial pain which point to cardiac origin: pain provoked or aggravated by physical activity, pain relieved by rest, bilateralism and a "pressure" or "burning" quality of pain. In the case of toothache or facial pain from suspected cardiac origin, the patient should be sent to the hospital for urgent cardiologic evaluation.

Further research is needed in order to investigate other clinical and pathological implications of this condition. Future research on pre-infarction symptoms should also include patients without chest pain.

# ACKNOWLEDGMENTS

This thesis would not have been possible without the support of many individuals and institutions. I owe my deepest gratitude to the following persons:

Professor **Annika Isberg**, principal supervisor, co-author and mentor. It was an honor for me to receive such a high quality research education and supervision, with outstanding guidance, advice, enthusiasm and extra engagement throughout this project.

Professor **Anders Waldenström**, assistant supervisor and co-author on papers III and IV, for his support, advice and fruitful research discussions.

Professor **Jeffrey Okeson**, co-author on papers I and II, for his continuous support, guidance and mentoring during the initial stages of this project.

Dr **Virginia Michelis**, co-author on papers I-IV, for critical review of the research protocol and manuscripts and for valuable personal engagement in the recruitment of patients with cardiac ischemia.

**Ramón Alvarez**, statistician, co-author on papers III and IV, for his dedicated statistical support throughout the project.

Dr **Donald Falace**, co-author on paper II, for his personal contribution regarding collection of patients with odontogenic pain and Dr **Mariela Lujambio**, for her assistance in recruiting patients with cardiac ischemia during the initial part of the study.

Dr **Rosana Muñiz**, co-author on paper IV, for her valuable assistance in the recruitment of patients with cardiac ischemia during the final stage of the project.

Dr **Fredrik Bryndahl** for his advice and talented support in the preparation of the drawing in paper IV and on the front cover.

**Ulrika Bertilsson**, Research Engineer, for her valuable help in the preparation of the figures in paper I and for her solicitude.

Dr **Per Erik Legrell** for proof reading of the thesis and for the constructive comments given.

Dr **Jan Ahlqvist**, Head of Department, for his kind support during this project.

Dr **Michael Henein**, for critical review and constructive criticism of papers III and IV and the thesis' frame text.

Dr **Alvaro Maglia**, colleague and past Dean at the School of Dentistry, Universidad de la República, Uruguay, for his continuous encouragement and advice ever since the beginning of the project.

Dr **Hanna Salé**, my fellow PhD student, for her attentive and thoughtful help regarding different matters throughout the years.

Dr **Eva Levring Jäghagen,** Dr **Tore Nilsson** and Mr **Magnus Johansson**, for their encouragement and help with various issues during my stays in Umeå.

Ms **Lillemor Hägglund**, Department Secretary, for her consideration, continuous support and exceptional administrative assistance throughout the years.

The entire **staff** at the Department of Oral and Maxillofacial Radiology, Umeå University, for always welcoming me whenever I worked at the Department.

Dr **Ricardo Lluberas**, **physicians** and **staff** at the Department of Cardiology, Hospital de Clínicas, Uruguay, for their valuable support during patient recruitment.

Dr **Daniel Fiandra**, Dr **Alfredo Fiandra**, **physicians** and **staff** at the Instituto Nacional de Cirugía Cardíaca (INCC), Uruguay, for their valuable support during patient recruitment.

Ms **Alyce Norder** for expert editing of the English text.

**Rachel Nicholl**, Medical Writer and researcher, for language review of papers III, IV and the thesis and the constructive criticism given.

The **Council** of the School of Dentistry, Universidad de la República, Uruguay, the past Dean Dr **Pablo Pebe** and the present Dean Dr **Hugo Calabria** for their continuous support throughout the project.

The past professors at the Department of General and Oral Physiology, Universidad de la República, Uruguay, the late Drs **Juan Boccardo** and **Edwin Betancor** as well as Drs **Horacio Fioresti** and **Morris Mizraji**, for their support and encouragement during the initial stage of my research activities.

My **colleagues** and **coworkers** at the Department of General and Oral Physiology, School of Dentistry, Uruguay, for their incredible support while I have been in Sweden working on this project.

The **staff** and **colleagues** at the Orofacial Pain Center, University of Kentucky, USA, for their support during my visits to the Center.

The entire **staff** at the School of Dentistry, Universidad de la República, Uruguay for their valuable support throughout the years.

Dr **María del Huerto Martirena**, Dean's academic assistant**,** for her support and assistance throughout the project.

Ms **Teresita Frugone** for her continuous support and outstanding assistance.

I would also like to thank my family. I am deeply grateful to my wife **Adriana**, my daughter **Micaela** and my son **Gabriel** for their incredible support and infinite patience during all these years. I also want to thank my parents **Berta** and **Pablo** and my brother **Bruno** for their great support and wise advices.

**This project received financial support from the following institutions:**

The School of Dentistry, Universidad de la República, Uruguay.
The Comisión Sectorial de Investigación Científica (CSIC), Universidad de la República, Uruguay.
The Medical Faculty, Umeå University, Sweden.
The Swedish Dental Society, Sweden.
The Swedish Medical Research Council (Project 6877), Sweden.

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