CARDIOVASCULAR AND SLEEP-RELATED CONSEQUENCES OF TEMPOROMANDIBULAR DISORDERS

NHLBI WORKSHOP

Sponsors:
National Heart, Lung and Blood Institute (NHLBI)
NHLBI Division of Heart and Vascular Diseases (DHVD)
NHLBI National Center on Sleep Disorders Research (NCSDR)

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FINAL REPORT

Participants

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Objectives

1. Review what is known about cardiovascular and sleep-related consequences of temporomandibular disorders (TMD)

    - Pathophysiology and clinical consequences of sleep and TMD
    - Physiology and biomechanics of breathing and swallowing
    - Neurological integration of the cardiovascular, respiratory, and pain pathways that influence these systems in health and in disease.
2. Identify gaps in current knowledge
3. Recommend future research priorities.

Pathophysiology and Clinical Consequences of Sleep and Temporomandibular Disorders

Temporomandibular Disorders – Definition and Prevalence

The term TMD refers to a collection of medical and dental conditions affecting the temporomandibular joint (TMJ) and/or muscles of mastication, as well as contiguous tissue components. Symptoms range from occasional discomfort to debilitating pain and severely compromised jaw function. The masticatory apparatus is not only involved in chewing and swallowing but also in other critical tasks, including breathing and talking. Specific etiologies such as trauma and degenerative arthritides underlie some forms of TMD but there is no common etiology or biological explanation. TMD is hence comprised of a heterogeneous group of health problems whose signs and symptoms are overlapping but not identical.

Although broad longitudinal and cross-sectional epidemiological studies have not been carried out, TMD is estimated to affect about 12% of the general population, representing more than 34 million Americans. The majority of those seeking treatment are women in their reproductive years. As for many other pain conditions, the clinical scenario of TMD also tends to be more severe in women than men. TM disorders are considered a serious health problem because many individuals lose their ability to hold regular jobs and to function productively even within the context of a household environment.

The current diagnostic taxonomies of TMD are based on signs and symptoms rather than on etiological or pathogenetic features. Depending on the practitioner and the diagnostic methodology employed, TMD has been used to characterize a wide range of conditions diversely presented as pain in the face or jaw joint area, masticatory muscle pain, headaches, earaches, dizziness, limited mouth opening due to soft or hard tissue obstruction, TMJ clicking or popping sounds, excessive tooth wear and other complaints. TMD remains to be classified in the larger context of other muscle and joint disorders or in the category of pain disorders (NIH Technology Assessment Conference, 1996). About half of all cases are attributed to conditions linked to the muscles of mastication; the remaining cases are classified as TMJ arthritides and/or internal derangements. Pain linked to the TMJ and/or muscles of mastication constitutes the essential criterion for case assignment. It often qualifies as “aching”, “throbbing”, “tiring” and exhausting. About 60-90% of cases appear to experience satisfactory resolution of symptoms with a range of interventions. In contrast, the remaining group of patients does not respond well to these treatments and continues to exhibit persistent pain. Comorbid complaints, such as problems with sleep, blood pressure and breathing are not uncommon for this group of TMD patients but have not been well characterized.

Reproductive age, female gender and to some extent trauma are the major risk factors for TMD. As identified by the NIH Technology Assessment Conference on TMD in 1996, there is a need for longitudinal studies of TMD as related to the natural history and to potential risk factors and using predictive and explanatory statistical methodologies. Prospective epidemiological research is needed to determine the clinical risk factors for TMD and their relationships to cardiovascular diseases. However, there are reasons to suspect that TMD patients are at greater risk for cardiovascular diseases. Many patients exhibit sleep dysfunction associated with persistent pain and inability to sleep on their side, but sleeping supine increases the risk for sleep disordered breathing. The effects of acute and persistent pain upon autonomic and motor control of these systems would be expected to impose further cardiovascular risk to these patients based upon what is already known about the effects of sleep disordered breathing.

Sleep Disordered Breathing – Definition and Prevalence.

There exists a wide range of conditions referred to as sleep disordered breathing (SDB) including obstructive sleep apnea, hypopnea (shallow breaths), and upper airways resistance syndrome. All patients with SDB have frequent arousals from sleep and resultant sleep deprivation. Patients with obstructive sleep apnea or hypopnea may have frequent and repetitive episodes of oxygen desaturation. The most common clinical symptoms are loud snoring, apneas witnessed by bed partners and excessive daytime sleepiness. In addition, the condition has been linked to delayed reaction times, difficulty maintaining vigilance and concentration, and to cardiovascular consequences.

Epidemiological data (Young et al. 1993, Wisconsin Sleep Cohort Study) suggest that sleep apnea/hypopnea is relatively common, with a prevalence rate of 2% in middle-aged women and 4% in middle-aged men based on a combination of SDB and excessive daytime sleepiness. Unlike TMD, men are more susceptible than women and sleep apnea/hypopnea is hence less common in pre-menopausal females. Asymptomatic sleep apnea/hypopnea occurs at much higher rates in men (24%) compared to women (9%), but it is not known what proportion of these individuals will eventually develop clinical disease or be at risk for cardiovascular disease. Clusters of families with OSA have also been identified. Obesity or being overweight is a predisposing factor. SDB is worsened by the use of alcohol and sleep-promoting medications. Young African Americans are more likely than whites to suffer from sleep-disordered breathing.

Clinical risk factors for SDB include male gender, increasing age, obesity, and increased neck circumference. Retrognathia, a condition that can result from TMJ arthritis, also constitutes a risk factor for SDB. In addition, several different craniofacial configurations such as a more caudally positioned hyoid and smaller anteroposterior dimensions of the lower face have been associated with a greater prevalence of SDB.

SDB has been associated with hypertension by both cross-sectional and longitudinal data, and cross-sectionally with ischemic heart disease, congestive heart failure and stroke. These cardiovascular consequences are independent of other risk factors such as obesity. Many of the risk factors for cardiovascular disease are the same as those for sleep apnea (SDB). Approximately 50% of patients with congestive heart failure have SDB. It is well known that left heart failure causes pulmonary congestion with exertional and positional orthopnea and paroxysmal dyspnea, and that these symptoms are exaggerated during sleep due to volume redistribution to the central circulation. Systemic hypertension and/or congestive heart failure can thus cause SDB or can be the consequence of SDB.

The Craniofacial Complex and its Impact on Control of Upper Airway Resistance and Cardiopulmonary Function

Jaw Biomechanics and Function

The temporomandibular joint (TMJ) is the articulation of the temporal bone with the condylar process of the mandible. An articular disk separates the articular surfaces of the two bony elements of the joint. During jaw opening, the mandibular condyle and disk slide forward onto the temporomandibular eminence as the condyle rotates about the disk. Because the mandible is a bone with a condylar process at both ends, movement about one TMJ impacts the structure and function of the contralateral TMJ. Movement of the mandible about the TMJ is complex; several muscles are arranged to produce multi-axial movements and they are subdivided into

neuromuscular compartments that produce different mechanical actions. These compartments are activated differently during the production of different oral behaviors, suggesting that they function as output elements used in different combinations by the nervous system. These muscles are complex and unique, containing fibers of phenotypes not found in limb muscles. They are smaller, and express myosin heavy chain isoforms found only in limb muscles during development. The cardiac alpha-myosin heavy chain isoforms of the masseter and temporalis muscles are unique to skeletal muscle and resemble heart muscle. Considerable sexual dimorphism has been identified in these muscles with regard to the slow and fast fibers types of the masseter. Males have predominately fast fiber types while females predominately slow fiber types. These sex differences arise in response to androgens in males but persist even in the absence of androgens.

Mandibular Movements, Upper Airway Resistance, Breathing and Swallowing

There appears to an associated increase in coughing in subjects with sleep apnea. Occlusion of the pharynx can force residual secretions into the glottis and trigger coughing reflexes, swallowing reflexes, and other reflexes that could contribute to the disorganization of breathing during sleep. In addition to the muscles of mastication, the tongue plays an important role in the coordinated events of swallowing and breathing. The integration of breathing and swallowing is tightly linked, and these events in turn are in some manner linked to blood pressure regulation. Each of these pathways has been studied by scientists in individual disciplines, but there is a need for interdisciplinary studies to determine the interactions of the peripheral and central neural pathways controlling breathing, chewing, swallowing, and cardiovascular events. The presence of pain in patients with TMD would be expected to seriously impact upon these reflex and motor pathways. Little is known about the role of tongue position and how this may be altered in subjects with altered jaw location and structure. Sleep state has been shown to alter the central modulation of the coordination of breathing, airway dynamics, swallowing, and associated cardiovascular events. Differences in central modulation of these events in subjects with sleep apnea and TMD need to be evaluated using sleep as a dynamic change in the state of the individual. Cardiovascular, neuroendocrine, respiratory and swallowing alterations in awake and sleeping subjects need to be studied in a systematic manner in both in animal models and human subjects.

Control of Upper Airway Collapsibility During Sleep

The upper pharyngeal airway in humans has relatively little bony or rigid support. Since there is variability in soft tissue and bony structures of the head and neck, there must be mechanisms in place that enable the pharyngeal dilator muscles to adjust for these anatomic differences. Animal and human studies indicate that there are at least three mechanisms to control the activity of the genioglossus muscle. *Firs*t, negative pressure has substantial impact on this muscle and a clear linear relationship exists between negative pressure in the airway and genioglossal activation. *Second*, there is pre-motor neuron input to these muscles from respiratory pattern generating circuits as shown by the pre-activation of these muscles that occurs prior to the development of negative pressure in the airway. *Third*, tonic activity in the muscle is consistently evident, although the mechanisms that determine the level of this activity have not been studied. During sleep, the mechanisms that control upper airway resistance are importantly impacted. Specifically, tonic activity drops markedly and the negative pressure reflex is substantially attenuated or completely lost. These findings have important implications in the pathophysiology of SDB.

It is well established that as upper airway obstruction increases during sleep, there is increased collapsibility of the airways. It has been found that patients with SDB have anatomically smaller airways and it is believed that this activates negative pressure reflexes leading to increased muscle activity. Combined with their abnormal anatomy, SDB patients generate negative pressure that activates upper airway muscles and reduces collapsibility.

Stimulation of the hypoglossal nerve leads to a considerable decrease in upper airway collapsibility. This suggests that electrical or pharmacological stimulation of the upper airway musculature might potentially alleviate upper airway obstruction during sleep.

Upper airway collapsibility during sleep has not been studied in patients with TMD dysfunction. However, because chronic craniofacial deep tissue pain and central neural plasticity are characteristic of these patients (see below) and it is known that neuromuscular activity importantly modulates upper airway collapsibility, it is likely that TMD patients would exhibit elevations in collapsibility and hence the co-morbid consequences of SDB. Studies are needed to assess these potential consequences of TMD.

Craniofacial/Deep Tissue Persistent Pain and Relationships to Cardiovascular and Pulmonary Function and Disease.

Injury to peripheral tissues following trauma or surgery often results in hyperalgesia that is characterized by increased sensitivity to painful stimuli. This is a common problem in patients with TMD. Until recently, it was thought that the increase in pain was due to changes at the site of injury but it is now known that it involves central nervous system hyper-excitability leading to long-term changes in the nervous system. Animal models of hyperalgesia produced by inflammation or nerve injury that mimic persistent pain conditions have shown that an increased neuronal barrage into the central nervous system (CNS) leads to central sensitization involving activation of excitatory amino acid transmitters and their receptors. The activation of N-methyl-D-aspartate (NMDA) receptors leads to influx of calcium into neurons, the activation of protein kinases, and phosphorylation of receptors. The net effect of these responses is increased gene expression of NMDA receptors, an alteration in the sensitivity of receptors, increased excitability, and an amplification of pain. These responses appear to be most robust in response to deep tissue injury such as occurs in TMD patients.

Modulation by descending pathways from the CNS importantly influences these events. Under normal conditions, the net effect of the descending neural projections from the brain stem to the spinal cord is to inhibit or counterbalance the hyper-excitability produced by tissue injury. It is now understood that this balance can shift to a net excitatory effect whereby descending modulation results in more hyper-excitability and more pain after injury. This central sensitization appears to be a prominent component in patients suffering from deep pain conditions such as TMD and fibromyalgia. It is believed that the diffuse nature and amplification of pain is in part due to this imbalance and that these findings have important functional implications relevant to the survival of the organism in response to the presence of persistent tissue injury. It is therefore now believed that persistent pain can be attacked both at the site of injury and where it is elaborated in the nervous system.

Alteration in Baroreceptor Activity - Impact on Pain, Autonomic Function, Motor Output, and Sleep:

Evidence has emerged that several regions of the CNS interact in complex ways to integrate sensory perception, autonomic function, motor output, and sleep architecture. The outcomes of a number of recent studies also suggest that several of the signs and symptoms associated with TMD may result, at least in part, from impairments in neural networks that coordinate the interplay between sensory systems, autonomic function, motor output, and sleep architecture. Many of the central pathways that are critically involved with the integration of these systems are regulated by visceral afferent input, including input from cardiopulmonary, carotid sinus, and aortic arch baroreceptors. In addition, abnormalities in the function and central integration of baroreceptor afferent information has been associated with abnormalities in pain perception, autonomic function, motor output, and sleep architecture, and thus may contribute to the development and maintenance of TMD and other related disorders (e.g., fibromyalgia). There is a need for additional studies that systematically examine whether abnormal baroreceptor function contributes to the pathogenesis of TMD.

Cardiovascular and Sleep-Related Consequences of TMD

General Rationale

Nearly 12% of the general population, primarily women, exhibits symptoms of TMD. These subjects are characterized by pain, restricted range of mandibular motion, altered jaw relationships including retrognathia, and the impact of pain on jaw motor function. The effects of chronic pain upon upper airways resistance and SDB are largely unknown but a close association is plausible. Based on current understanding of neural pathways, it is evident that there exist important central interactions between pain pathways and the motor control of respiration, swallowing, and cardiovascular (CV) functions. However, the precise relationships and the manner of integration of these complex pathways are poorly understood at this time.

Subjects with SDB exhibit increased risk for cardiovascular diseases that is, to some extent, related to repetitive episodes of nocturnal hypoxemia. However, to the extent that increased cardiovascular risk in patients with SDB is related to factors other than hypoxemia, such as sleep disruption, it is possible that subjects with TMD would be similarly predisposed to increased risk of CV diseases, including hypertension, heart failure and stroke.

Epidemiological data are needed to determine the level of increased risk for cardiovascular diseases and carefully designed basic studies are required to determine the mechanisms responsible for these events.

Specific Rationale

1. Structural and neuromuscular events can lead to increased upper airway resistance and SDB and perhaps also to TMD.

2. The neuromuscular mechanisms that control upper airway resistance are importantly impacted in patients with SDB and it is likely that an imbalance of the neural pathways controlling respiration and swallowing would occur in patients with chronic pain emanating from the craniofacial structures.

3. Pain is the principal clinical feature that defines TMD. Although an understanding is evolving with regard to CNS plasticity of the brain exposed to chronic pain, there is little understanding of how the central pathways involved in pain modify the integrated output of the autonomic and motor responses to the heart, vasculature, and pulmonary systems.

GAPS IN CURRENT KNOWLEDGE

1. Although there is reason to believe that there may be significant CV and sleep-related consequences of TMD, data are required to test the validity of these proposed associations.

2. Prospective and longitudinal data pertaining to the natural history of TMD are required to understand the causes, progression and co-morbidities of this disorder.

3. Although there is reason to believe that associations may exist between SDB and TMD, basic epidemiological data are needed to quantify and test the validity of such proposed associations.

4. The effects of TMD on the quality of sleep and sleep architecture need to be systematically defined.

5. Levels of muscle tone in subjects with TMD during wakefulness and sleep need to be defined using well-defined patient groups.

6. It is unknown whether TMD patients can appropriately recruit active pathways to control upper airway resistance during sleep. Reflex deficits, if any, need to be characterized and the influence of persistent pain evaluated in a systematic manner.

7. The “sleep architecture” of subjects with TM disorders under “challenged” conditions using standard stressors needs to be defined. This includes muscle activity of the tongue (genioglossus), pharynx, masseter muscles, blood pressure and cardiovascular responses, respiratory responses, and swallowing.

8. Blood pressure alterations during sleep in patients with TMD are unknown. Is the normal diurnal rhythm altered in these subjects (“dippers” versus “non-dippers”)?

9. It is unknown if peripheral afferent neural pathways are altered in patients with TMD due to the effects of pain on muscle stretch receptor afferents or autonomic afferents such as carotid baroreceptors or chemoreceptors.

10. It is unknown whether alterations in cardiopulmonary, carotid sinus, and aortic arch baroreceptor function contribute to signs and symptoms associated with TMD and related disorders.

11. Research is needed to better define central neural pattern generators controlling cardiopulmonary rhythms and swallowing patterns in subjects with TMD and SDB.

12. The effect of gender and hormones upon all of these complex pathways is unknown.

13. Neuromuscular control of the mandible and pharyngeal dilator muscles may be altered during sleep in patients with TMD. This needs to be determined.

14. Myalgia and fibromyalgia are symptoms that can occur in otherwise healthy subjects with sleep deprivation. It is not known, however, whether the lack of sleep in TMD patients exacerbates the progression of disease?

15. Sleep state has been shown to alter central modulation of the coordination of breathing, airway dynamics, swallowing, and associated cardiovascular events. Differences in central modulation of these events in subjects with SDB and TMD need to be evaluated using sleep as a dynamic state change.

RESEARCH RECOMMENDATIONS

1. Basic epidemiological data are needed to determine CV and sleep-related consequences of TMD. It is imperative that both longitudinal and cross-sectional studies be carried out to determine the relevant co-morbidities.

2. Prospective clinical studies are needed to determine if TMD constitutes a risk factor for CV diseases. It is important to evaluate the effects of gender, age and hormones on these relationships. .

3. Standardized assessment paradigms of TMD patients must be developed based on modalities of pain, muscle function, autonomic function, sleep, and cardiovascular/ pulmonary/ swallowing characteristics.

4. Studies are needed to understand the shared biomechanical aspects of patients with TMD and SDB. Basic experimental studies are required to better understand the integrated biomechanics and control (active and passive) of breathing and cardiovascular function.

5. Basic studies are required to understand the neural integration of pathways related to pain, breathing, cardiovascular function, and sleep. This includes efforts to identify genetically modified model organisms that mimic various aspects of the human conditions based on gene modification (gene deletions or addition; chromosomal substitution; chemical/radiation mutagenic studies, etc.). Muscle fatigue studies (e.g. swimming rats/hyperalgesia), persistent craniofacial pain paradigms, etc. are needed to study the state-dependent nature of these stressors upon quality of sleep and CV disorders.

6. Basic animal and clinical studies are required to examine the capacity of cardiopulmonary, carotid sinus and aortic arch baroreceptor systems to regulate pain, autonomic function, motor function and sleep. Studies should also be conducted to determine whether impairments in baroreceptor function are associated with and/or enhance the development of persistent pain conditions in animal models of TMD and in TMD patients.

7. The integration of proprioception and nociception in the pattern generator circuitry of chewing need to be explored. The circuitry of chewing, swallowing and respiration needs to be explored

8. The role of gender and hormonal regulatory systems upon all of these pathways must be carefully explored given the large prevalence of TMD in females in their reproductive years.

9. New investigative tools (invasive and noninvasive) are needed to assess temporomandibular muscle and joint function, neural pathways, swallowing, respiration and related cardiovascular functions. New techniques for imaging these pathways are required. These should take advantage of novel uses of biomaterials and nanotechnology techniques. Such technologies should be developed for use as nano-sensors of muscle and nerve activity, for imaging of airway and esophageal passages, for chronic delivery of molecules modulating pathway functions related to sleep, respiration, the heart, and blood vessels.

AGENDA

Allen W. Cowley, Jr., Ph.D.
Chair, Working Group

MONDAY, DECEMBER 3, 2001

4:30	Welcome	Claude Lenfant, MD
	Charge to the Working Group	Allen W. Cowley, Jr., PhD
SESSION 1	*PATHOPHYSIOLOGY AND CLINICAL CONSEQUENCES** *Moderator: Allen W. Cowley, Jr., PhD*	
4:45	Mechanisms Relating Sleep Disordered Breathing to Hypertension, Heart Failure And Stroke	T. Douglas Bradley, PhD
5:20	Temporomandibular Disorders: A Clinical Perspective	Christian Stohler, DDS, PhD
5:55	Overview of Temporomandibular Structure and Mechanics	Arthur English, PhD
6:30	GENERAL DISCUSSION	
7:00	ADJOURN	

TUESDAY, DECEMBER 4, 2001

SESSION 2	*PHYSIOLOGY AND BIOMECHANICS*** *Moderator: John Watson, PhD*	
8:00	Bioengineering Design Considerations	John Watson, PhD
8:30	Effects of Passive Mandibular Movements on Upper Airway Resistance	John Remmers, MD
9:00	Neuromuscular Control Of Upper Airway Collapsibility During Sleep	Alan Schwartz, MD
9:30	GENERAL DISCUSSION	
10:00	*Break*	
SESSION 3	*NEUROLOGICAL INTEGRATION*** *Moderator: Ronald Dubner, DDS, PhD*	
10:15	Reflexes Generated in Upper Airway	David P. White, MD

10:45	The Response Of The Nervous System To Persistent Tissue Injury	Ronald Dubner, DDS, PhD
11:15	Coordination of Breathing and Swallowing	Brad Thach, MD John Remmers, MD
11:45	GENERAL DISCUSSION	
12:15	*Lunch*	

*SESSION 4: SLEEP, BREATHING AND CARDIOVASCULAR INTERACTIONS***
Moderator: Stuart F. Quan, MD

1:15	Pain/Baroreceptors/Arterial Pressure	William Maixner, DDS, PhD
1:45	What Is Sleep Disordered Breathing and What Are The Risk Factors Related to Cardiovascular Disease?	Stuart F. Quan, MD
2:15	GENERAL DISCUSSION	

SESSION 5 CONCLUDING DISCUSSION AND FINAL RECOMMENDATIONS
Moderator: Allen W. Cowley, Jr., PhD

2:30	Discussion and Recommendations	All Participants
4:30 PM	ADJOURN	