Hypocapnia in Patients with Chronic Neck Pain Association with Pain, Muscle Function, and Psychologic States

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ORIGINAL RESEARCH ARTICLE

Hypocapnia in Patients with Chronic Neck Pain

Association with Pain, Muscle Function, and Psychologic States

ABSTRACT

Dimitriadis Z, Kapreli E, Strimpakos N, Oldham J: Hypocapnia in patients with chronic neck pain: association with pain, muscle function, and psychologic states. Am J Phys Med Rehabil 2013;92:746–754.

Objective: The aim of this study was to investigate whether patients with chronic neck pain have changes in their transcutaneous partial pressure of arterial carbon dioxide ($P_{tc}CO_2$) and whether other physical and psychologic parameters are associated.

Design: In this cross-sectional study, 45 patients with chronic idiopathic neck pain and 45 healthy sex-, age-, height-, and weight-matched controls were voluntarily recruited. The participants' neck muscle strength, endurance of the deep neck flexors, neck range of movement, forward head posture, psychologic states (anxiety, depression, kinesiophobia, and catastrophizing), disability, and pain were assessed. $P_{tc}CO_2$ was assessed using transcutaneous blood gas monitoring.

Results: The patients with chronic neck pain presented significantly reduced $P_{tc}CO_2$ ($P < 0.01$). In the patients, $P_{tc}CO_2$ was significantly correlated with strength of the neck muscles, endurance of the deep neck flexors, kinesiophobia, catastrophizing, and pain intensity ($P < 0.05$). Pain intensity, endurance of the deep neck flexors, and kinesiophobia remained as significant predictors into the regression model of $P_{tc}CO_2$.

Conclusions: Patients with chronic neck pain present with reduced $P_{tc}CO_2$, which can reach the limits of hypocapnia. This disturbance seems to be associated with physical and psychologic manifestations of neck pain. These findings can have a great impact on various clinical aspects, notably, patient assessment, rehabilitation, and drug prescription.

Key Words: Blood Gases, Carbon Dioxide, Hypocapnia, Neck Pain

Chronic neck pain is one of the most frequent musculoskeletal complaints, and it is estimated that approximately two-thirds of the population will experience neck pain at some time in their lives.[1] Patients with chronic neck pain present with a number of physical and psychologic constraints including weakness and fatigue of the neck muscles[2,3]; reduced cervical range of movement (ROM)[4]; altered proprioception[5]; forward head posture (FHP)[6]; and psychologic states such as anxiety, depression, catastrophizing, and kinesiophobia.[7–9] All of these manifestations may constitute factors that influence respiration by biochemical and biomechanical mechanisms, resulting in changes in blood chemistry.[10]

Blood gases are important indicators of respiratory function, and changes in blood chemistry are associated with disturbed acid/base balance and respiratory disorders.[11] There is evidence that changes in blood gases can be observed not only in cardiorespiratory diseases but also in pain conditions. Nishino et al.[12] found that experimental pain induced by tourniquet inflation increases ventilation and decreases end-tidal carbon dioxide tension. Similar changes were observed by Borgbjerg et al.[13] using the same pain stimulus technique. A placebo study that used pain stimulus infusions of hypertonic saline into the masseter muscles also reveals a pain-specific stimulation of respiration.[14]

Musculoskeletal pain conditions have also been found to be associated with changes in blood gases. Patients with low back pain[15] have been found to have reduced $Paco_2$. In agreement with these findings, McLaughlin et al.[16] used capnography and found existence of hypocapnia in a mixed sample of patients with spinal pain.

In patients with chronic neck pain, little is known about blood gases. Furthermore, the associations of these changes in blood chemistry with the physical and psychologic outcomes of neck pain are completely unexplored. Understanding the changes in blood chemistry of patients with chronic neck pain could lead to a deeper insight into the changes occurring as a result of neck pain. Current practices regarding the usual assessment, treatment, and drug prescription of patients with neck pain could be also improved. Therefore, the primary aim of this study was to examine whether patients with chronic neck pain have changes in their transcutaneous partial pressure of arterial carbon dioxide ($P_{tc}co_2$). This study additionally aimed to examine which neck pain symptoms and psychologic states are associated with these changes.

METHODS

Subjects

Forty-five patients with chronic idiopathic neck pain (men/women, 13/32; age, 35.9 ± 14.5 yrs) and 45 healthy sex-, age-, height-, and weight-matched controls (men/women, 13/32; age, 35.4 ± 14 yrs) were conveniently recruited from every available area in Central Greece. Sample size calculation revealed that, for the main hypothesis (differences in $P_{tc}co_2$ between the groups), 26 subjects per group were needed (two-tailed hypothesis, $\alpha = 0.05$, $\beta = 0.8$, $d = 0.8$). However, 45 subjects per group were recruited to increase statistical power and to take into account the potential for missing data.

A health questionnaire was used to screen for eligibility criteria. Details of inclusion and exclusion for both the patients and the healthy subjects have been described in a previous publication.[17] This study was approved by the ethics committee of the Department of Physiotherapy, School of Health and Caring Professions, Technological Educational Institute of Lamia, Greece, and the University of Manchester ethics committee, Manchester, United Kingdom.

Questionnaires

The pain intensity of the patients with chronic neck pain was assessed using visual analog scales.[18] The visual analog scale was presented graphically as a 10-cm line, and the participants were requested to mark the point that better described their pain intensity. One visual analog scale was used for describing their usual pain intensity; and one, for describing their pain intensity at the start of the measurements. The start of each of these scales represented the "no pain" condition, whereas their end represented the "worst imaginable pain" condition. The psychometric properties of the visual analog scale have been widely studied, and it is the most usual assessment tool for assessing pain intensity.[18–20] Pain-induced disability was assessed using the Neck Disability Index (NDI).[21] This questionnaire includes ten items. The total NDI score may range from 0 (no disability) to 50 (complete disability). The NDI has been found to have good reliability and validity.[22,23] The Baecke Questionnaire of Habitual Physical Activity is an instrument with satisfactory psychometric properties[24] and was used for assessing physical activity level. The Baecke Questionnaire of Habitual Physical Activity score may range from 3 (no physical activity) to 15 (high physical activity).

Psychologic states were assessed using the cross-cultural validated Hospital Anxiety and Depression Scale,[25] the Tampa Scale for Kinesiophobia,[26] and the Pain Catastrophizing Scale[27] in a randomized order. The Hospital Anxiety and Depression Scale includes two 7-item subscales. The first subscale assesses anxiety, and the second subscale assesses depression. Each subscale score may range from 0 (not anxious or depressed) to 21 (highly anxious or depressed). The Tampa Scale for Kinesiophobia is a 17-item questionnaire, and its score may range from 17 (not kinesiophobic) to 68 (highly kinesiophobic). The Pain Catastrophizing Scale includes 13 items. Its score may range from 0 (no catastrophizing) to 52 (high catastrophizing). The Tampa Scale for Kinesiophobia, the Pain Catastrophizing Scale, and the Hospital Anxiety and Depression Scale have established psychometric properties in patients with musculoskeletal disorders.[28–30]

Blood Gases Recording

Blood gases were recorded using transcutaneous blood gas monitoring (TCM40; Radiometer, Copenhagen, Analis, Belgium). The TCM40 was firstly calibrated, according to the manual instructions, through a removable calibration gas cylinder for approximately 5 mins for each participant separately. Then, the placement area was shaved and cleaned with alcohol,[31] and a fixation ring was applied 5 cm below the middle of the left clavicle.[31,32] The $P_{tc}CO_2$ electrode was then attached to the fixation ring using a special electrolyte solution for better conductivity. The electrode was set at 43°C to simultaneously increase skin blood flow and avoid any thermal injury.[33,34] During the recording, the participants were asked to breathe normally from a comfortable sitting position without speaking. The values of $P_{tc}CO_2$ were recorded after a 20-min stabilization period because $P_{tc}CO_2$ initially presents high values because of an initial CO_2 overshoot.[35,36] The values were recorded by calculating the mean $P_{tc}CO_2$ during the last 5-min time frame.[36] Transcutaneous assessment has been found[37–42] to be a valid and reliable noninvasive method for recording $P_{tc}CO_2$. TCM is also a valid and reliable transcutaneous assessment tool[31,32,43,44] of $P_{tc}CO_2$. The $P_{tc}CO_2$ values obtained by TCM present a high correlation with gazometric values[43] ($r = 0.87$) and minimal bias[31] (0.6 mm Hg).

Neck Function Assessment

The neck function assessment included assessment of the FHP, cervical ROM, strength of the neck muscles, and endurance of the deep neck flexors. The FHP was assessed by calculating the craniovertebral angle through lateral photographs (digital color camera, HDR-SR11E; Sony, Belgium).[45]

The Zebris ultrasound-based motion analysis system (Zebris Meditchnic GmbH, Isny, Germany) was used for assessing cervical ROM from a standing position in all neck movements.[46] A custom-made isometric neck dynamometer was used for assessing strength of the neck flexors and extensors from a standing position.[47] Endurance of the deep neck flexors was examined using the craniocervical flexion test.[48] Details about the assessment procedures and their corresponding reliability values are provided in the previous publication.[17]

Data Analysis

Differences between the groups were examined using paired t tests. Correlations between the variables were examined using Pearson correlation coefficients. Finally, a backward stepwise multiple regression method (removal, 0.1) was selected for constructing a prediction model for $P_{tc}CO_2$ in the patients with chronic neck pain. The predictors of the model were selected to be musculoskeletal and psychologic parameters that are theoretically supported to influence respiratory function.[10] Their selection was independent of their significance during univariate analysis. These predictors were the strength of the neck extensors, endurance of the deep neck flexors, sagittal ROM, craniovertebral angle, usual pain intensity, anxiety, depression, kinesiophobia, and catastrophizing. Patients with missing data were excluded from each analysis (with their matched controls) concerned with the variable from which these data were missing. The data lost were completely at random, and these were missing for left rotation and left lateral flexion ROM (one patient, software problems), endurance of the deep neck flexors (one patient, no glasses), FHP (one control, hair clip broken), $P_{tc}CO_2$ (two controls, TCM problems).

The significance level for all statistical tests was defined as equal to 0.05. The analysis was performed using the Statistical Package for the Social Sciences (version 17).

RESULTS

The two groups were found to have similar anthropometric characteristics ($P > 0.05$; Table 1). The patients with chronic neck pain were also found to have reduced strength of the neck extensors, reduced ROM in all movement planes, and reduced endurance of the deep neck flexors ($P < 0.05$).

TABLE 1 Sample characteristics

	Patients with Neck Pain	Controls
Sex[a] (men/women), *n*	13/32	13/32
Age,[a] mean (SD), yrs	35.9 (14.5)	35.4 (14)
Height,[a] mean (SD), cm	165.8 (9.2)	167.1 (8.7)
Weight,[a] mean (SD), kg	71.6 (16)	72.3 (15.2)
BMI,[a] mean (SD)	25.9 (4.5)	25.8 (4.4)
Physical activity[a] (BQHPA)	7.9 (1.3)	7.6 (1.4)
Usual pain intensity, mean (SD), mm	45.5 (18.8)	—
Current pain intensity, mean (SD), mm	19.3 (19.1)	—
Pain chronicity, mean (SD), mos	69.6 (57.6)	—
Disability (NDI), mean (SD)	10.6 (5.2)	—
Side of pain (L/R/B), *n*	12/12/21	—
Headaches, *n*	32	—

[a] $P > 0.05$.

BMI indicates body mass index; BQHPA, Baecke Questionnaire of Habitual Physical Activity; L/R/B, left/right/both.

Strength of the neck flexors presented a trend to be reduced. Craniovertebral angle, anxiety, and depression were not significantly different between the groups[17] ($P > 0.05$).

The difference in $P_{tc}CO_2$ between the two groups is presented in Table 2. The patients with chronic neck pain were found to have decreased $P_{tc}CO_2$ ($P < 0.01$) in comparison with the healthy controls. Nineteen patients were found to have $P_{tc}CO_2$ lower than 35 mm Hg.

Table 3 shows that $P_{tc}CO_2$ was significantly correlated with strength of the neck flexors ($r = 0.34$) and extensors ($r = 0.35$), endurance of the deep neck flexors ($r = 0.31$), usual pain intensity ($r = 0.34$), kinesiophobia ($r = 0.35$), and catastrophizing ($r = 0.3$; $P < 0.05$). All the other correlations were not significant ($P > 0.05$).

After the common input of all the potential predictors into a model for the prediction of $P_{tc}CO_2$, sagittal ROM (B = 0.01; β = 0.01; part correlation, 0.01; $P = 0.95$), catastrophizing (B = 0.02; β = 0.07; part correlation, 0.05; $P = 0.71$), anxiety (B = 0.12; β = 0.19; part correlation, 0.15; $P = 0.27$), depression (B = 0.1; β = 0.14; part correlation, 0.11; $P = 0.41$), strength of the neck extensors (B = 0.06; β = 0.17; part correlation, 0.15; $P = 0.28$), and craniovertebral angle (B = 0.07; β = 0.13; part correlation, 0.13; $P = 0.35$) were successively removed from the model. Endurance of the deep neck flexors (part correlation, 0.28; $P = 0.046$), kinesiophobia (part correlation, 0.29; $P = 0.039$), and pain intensity (part correlation, 0.27; $P = 0.049$) remained as significant predictors into the model (Table 4).

The constructed model was found to significantly fit the data overall ($P < 0.01$). The multiple correlation coefficient was found to be satisfactory ($R = 0.53$, $R^2 = 0.28$, adjusted $R^2 = 0.23$). Multicollinearity was not a problem (tolerance, >0.97). Further analysis showed that the assumption of independent errors (Durbin-Watson statistic, 1.95), the assumptions of homoscedasticity and linearity (plot of standardized residuals against standardized predicted values), and the assumption of normally distributed errors (histogram with a superimposed normal curve) had been met. No influential outliers were recognized.

DISCUSSION

The patients with chronic neck pain have demonstrated reduced strength of their respiratory muscles in comparison with the healthy controls.[17] The findings of the current study show that these patients also have reduced $P_{tc}CO_2$. Furthermore, their $P_{tc}CO_2$ was found to be correlated with pain intensity, strength of the neck muscles, endurance of the deep neck flexors, kinesiophobia, and catastrophizing. However, the regression analysis showed that only pain intensity, endurance of the

TABLE 2 Differences in blood gases between the patients with chronic neck pain and the healthy controls

	Patients with Neck Pain	Controls	Mean Difference (95% CI)	*r*
$P_{tc}CO_2$, mean (SD), mm Hg	34.9 (2.9)	37.3 (3.5)	2.4 (3.9 to 1)[a]	0.46

[a] $P < 0.01$.

CI indicates confidence interval.

TABLE 3 Correlations between $P_{tc}CO_2$ and chronic neck pain complaints

	$P_{tc}CO_2$
	Pearson *r*
Strength of neck extensors	0.35[a]
Strength of neck flexors	0.34[a]
Endurance of deep neck flexors	0.31[a]
ROM in sagittal plane	0.08
ROM in frontal plane	0.05
ROM in transverse plane	0.04
Craniocervical angle	0.14
Usual pain intensity	0.34[a]
Current pain intensity	0.14
NDI	0.19
Anxiety	0.12
Depression	0.13
Kinesiophobia	0.35[a]
Catastrophizing	0.3[a]

[a] $P < 0.05$.

deep neck flexors, and kinesiophobia have significant unique contribution to the prediction of $P_{tc}CO_2$.

The pain-related disturbances of the blood gases found in this study are also supported by other researchers. Studies in experimental pain conditions[12–14] provide evidence to support that experimental pain can lead to stimulation of respiration and decreased $PaCO_2$. In addition, studies in musculoskeletal pain conditions[15,16] provide further support to the findings because decrease in $PaCO_2$ was also observed.

The factors found to be associated with and to predict $P_{tc}CO_2$ fully comply with the mechanisms believed to lead to $P_{tc}CO_2$ drop. Although correlations cannot provide evidence about causality and can support only bidirectional associations or associations related to a third variable, a significant correlation in parallel with knowledge of physiology and biomechanics can lead to sound beliefs about the causes of a change.[49] Usual pain intensity experienced by the patients with chronic neck pain was found to be associated with the reduction of $P_{tc}CO_2$. The biochemical influences of pain are believed to be one key factor for this reduction. Pain results in the release of pain neurotransmitters, such as substance P, which have stimulatory effects on respiratory function leading to hyperventilation and $PaCO_2$ reduction.[50] Another explanation about the connection of pain and $P_{tc}CO_2$ reduction might be the self-induced hyperventilation. Considering that hyperventilation has analgesic effects,[51] this might be a chronic adaptation of patients with chronic neck pain to decrease their pain intensity. However, although this mechanism can help those with neck pain to self-regulate their pain intensity, this mechanism leads them to a hypocapnic state. This adaptation may finally become a permanent condition because of a reprogramming of the respiratory centers.[11]

$P_{tc}CO_2$ reduction was also found to be associated with psychologic manifestations of neck pain. Kinesiophobia and catastrophizing seem to be the two psychologic states that are related to the presence of $P_{tc}CO_2$ abnormalities. However, although both kinesiophobia and catastrophizing are significantly correlated with $P_{tc}CO_2$, catastrophizing was not included in the prediction model of $P_{tc}CO_2$. The exclusion of catastrophizing may be attributed to its low unique contribution to the model because catastrophizing has a similar theoretical concept with kinesiophobia and causes increased pain anticipation.[52] Thus, psychologic compromise and especially kinesiophobia seem to be the second main reason for $P_{tc}CO_2$ reduction in patients with chronic neck pain because its existence can exert stimulatory effects on respiration and increase inventilation mainly because of adrenaline release.[53,54]

Anxiety is a psychologic state that is closely related to ventilation and seems to play an important role for the development of disorders such as hyperventilation syndrome.[53,55,56] Anxiety can affect the autonomous nervous system and directly influence respiratory function because of the release of adrenaline, causing hyperventilation, and,

TABLE 4 Regression model for the prediction of $P_{tc}CO_2$

$P_{tc}CO_2$ Prediction	B (95% CI)	SE B	β
Constant	33.17 (24.34 to 42)[b]	4.37	
Endurance	0.34 (0.01 to 0.68)[a]	0.17	0.28
Kinesiophobia	0.12 (0.23 to 0.01)[a]	0.06	0.29
Usual pain	0.04 (0.08 to 0)[a]	0.02	0.28

This table presents the beta values (B) with their 95% confidence intervals (CIs) and their standard error (SE B) as well as the standardized beta values (β) for the prediction of $P_{tc}CO_2$ in the patients with chronic neck pain.

[a] $P < 0.05$.

[b] $P < 0.001$.

consequentially, a decrease[53,57,58] in $PaCO_2$. Thus, although this study did not reveal any significant correlation between anxiety and $P_{tc}CO_2$, its role in the development of hypocapnia cannot be ignored.

The association of $P_{tc}CO_2$ with cervical muscle function is observed by its significant correlation with strength of the neck muscles and endurance of the deep neck flexors. The removal of neck muscle strength from the model can be potentially explained by its common contribution with the endurance of the deep neck flexors to the prediction of $P_{tc}CO_2$. In the current study, the function of the cervical muscles of the patients with chronic neck pain was affected because there are weakness of their neck muscles and fatigue of their deep neck flexors.[17] Weakness of the neck muscles may directly influence respiratory function because the sternocleidomastoid, the trapezius, and the scaleni participate in both neck movement and inspiration.[59] In addition, the weakness of the neck muscles is believed to lead to changes in force-length curves and muscle imbalances,[60] causing uncontrolled movement[61] with a consequential change of rib cage mechanics.[10] Furthermore, it is suggested that the dysfunction of deep neck musculature leads to segmental instability, affecting the kinetic control not only of the neck area but also of neighboring articulations such as the thoracic spine, which, in turn, might lead to changes in rib cage mechanics.[10,61,62] These changes in rib cage mechanics might alter the force-length curves of the related respiratory muscles such as the diaphragm, the abdominals, and the intercostals, leading them to adapted contraction patterns.[10]

These biomechanical changes are believed to be the main reasons for the respiratory weakness observed in patients with chronic neck pain.[17,63] According to Pass and Bolton,[64] respiratory muscle weakness might lead to reduction of lung volumes because the muscles do not have the appropriate strength to fully expand the lungs. This may lead to a ventilation/perfusion mismatching because the changes in ventilation are not accompanied by similar changes in lung perfusion. The blood shunt deriving from this ventilation/perfusion mismatching may result in hypoxia. This hypoxia can stimulate respiratory function and may explain the increased respiratory rate in patients with chronic neck pain,[65] resulting in reduction[64] of $PaCO_2$.

Although this mechanism seems to be a reasonable mechanism for the development of hypocapnia, the existence of hypoxia in patients with chronic neck pain is supported neither from the findings of the current study nor from the findings of any other known research. However, this association could be alternatively explained by viewing muscle dysfunction as a result of hypocapnia.[66,67] More specifically, hypocapnia may lead to increased excitability of the nerves, the muscles, and the neuromuscular junctions. This increased excitability may be attributed to the reduction of the free calcium ion concentration in the plasma as a result of the respiratory alkalosis accompanying hypocapnia. These neurophysiologic events may finally lead to an increase in reflex activities and muscle tone, predisposing to muscle fatigue.[66] However, it is apparent that in either case, the association of neck muscle dysfunction with hypocapnia requires further investigation.

The patients with chronic neck pain were found to have their $P_{tc}CO_2$ reduced, 2.4 mm Hg, in comparison with the healthy controls. This difference is higher than a difference of 2 mm Hg, which has been used for defining changes in $PaCO_2$ after interventions.[68] The small bias of transcutaneous assessment[31] of $PaCO_2$ suggests that the $P_{tc}CO_2$ values measured in the sample of this study are quite similar to the values that would have been obtained using direct blood sampling.

This study also shows that 42% of the patients had $P_{tc}CO_2$ lower than 35 mm Hg, which is the defining value for the existence of hypocapnia. Hypocapnia is a quite serious condition that may affect a number of body systems including the musculoskeletal, cardiorespiratory, and gastrointestinal systems.[69,70] Among the other symptoms, hypocapnia-based headaches are of special interest because this mechanism may be an alternative explanation of cervicogenic headache. Thus, cephalalgia observed in patients with chronic neck pain may be the result of cerebral vasoconstriction caused by hypocapnia-based alkalosis.[11,70]

The results of this study can be applied to patients with mild neck pain and disability. Although it is believed that the results are also relative to patients of a more severe condition, these cannot be absolutely accepted. The reason is because patients of more severe pain and disability may consume drugs that affect the blood chemistry.[71] Furthermore, the findings of this study are concerned with a Greek population, and how well these can generalize to people of different nationalities is unknown. This is mainly because of the potentially different experience of pain from people of different cultures and socioeconomic status. However, the use of cross-cultural validated questionnaires is expected to have importantly reduced the threats to external validity.

The changes in $P_{tc}CO_2$ observed in the patients with chronic neck pain give rise to important clinical implications about assessment, treatment, and

drug prescription. The assessment of patients with chronic neck pain should not focus merely on their neuromusculoskeletal impairments, but it should additionally include assessment of their respiratory function. Similarly, therapists are advised to adopt a more global consideration of the human body during the development of their therapeutic protocols, including also techniques for the improvement of patients' respiratory function. Finally, considering the effects of drugs on respiration,[72] these are advised to be prescribed in a more attentive and controlled manner.

One area of further study could be the examination of the role of proprioception in this respiratory dysfunction because it believed to be related to the dysfunction of the respiratory system.[10] However, before the examination of its role, reliable measurement protocols should be developed, the lack of which did not permit its assessment in the current study. Furthermore, randomized controlled trials are advised to be performed to understand whether the addition of respiratory physiotherapy, such as breathing reeducation exercises, into the usual treatment of patients with chronic neck pain can lead to a better therapeutic outcome. Future randomized controlled trials can also examine the effectiveness of management strategies for muscle function, pain, and kinesiophobia on respiratory function. Finally, new studies should be directed toward the development of classification systems for clearly understanding who exactly among patients with neck pain are more prone to develop hypocapnia. The answering of these questions by future researchers could help not only to enhance the scientific knowledge in this relatively unexplored area but also to promote optimal therapeutic protocols and to provide the foundations for a better clinical reasoning.

Despite the originality and the importance of these findings, there are some limitations that should be carefully considered. The potential for bias cannot be excluded because of the nonrandomized character of the sample recruitment method used and the lack of blinded assessors. Furthermore, although transcutaneous assessment of $P_{tc}CO_2$ can provide valid and reliable measurements, the valid noninvasive assessment of transcutaneous partial pressure of arterial oxygen was not possible. The data obtained from this study do not show any change in transcutaneous partial pressure of arterial oxygen or oxygen saturation between the groups, but the validity of such findings is questionable and was not included in the study. Future studies should consider the use of direct blood sampling, which was not possible in this study because of practical and deontological issues.

CONCLUSIONS

It is time to reconsider whether chronic neck pain is a simple musculoskeletal dysfunction. The preliminary results show that these patients also present disturbances in their respiratory function, as depicted by the changes in blood chemistry. The main reasons that are associated with the development of hypocapnia in patients with chronic neck pain seem to be the dysfunction of their neck muscles, the biochemical influences of pain, and psychologic states such as kinesiophobia. Clinicians are strongly advised to consider this respiratory dysfunction during the management of patients with chronic neck pain and appropriately address their assessment and interventions.

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REFERENCES

1. Cote P, Cassidy JD, Carroll L: The factors associated with neck pain and its related disability in the Saskatchewan population. *Spine* 2000;25:1109–17
2. Chiu TT, Lo SL: Evaluation of cervical range of motion and isometric neck muscle strength: reliability and validity. *Clin Rehabil* 2002;16:851–8
3. Harris KD, Heer DM, Roy TC, et al: Reliability of a measurement of neck flexor muscle endurance. *Phys Ther* 2005;85:1349–55
4. Rix GD, Bagust J: Cervicocephalic kinesthetic sensibility in patients with chronic, nontraumatic cervical spine pain. *Arch Phys Med Rehabil* 2001;82:911–9
5. Cheng CH, Wang JL, Lin JJ, et al: Position accuracy and electromyographic responses during head reposition in young adults with chronic neck pain. *J Electromyogr Kinesiol* 2010;20:1014–20
6. Lau HMC, Chiu TTW, Lam TH: Clinical measurement of craniovertebral angle by electronic head posture instrument: a test of reliability and validity. *Man Ther* 2009;14:363–8
7. Hill JC, Lewis M, Sim J, et al: Predictors of poor outcome in patients with neck pain treated by physical therapy. *Clin J Pain* 2007;23:683–90
8. Mantyselka P, Lupsakko T, Kautiainen H, et al: Neck-shoulder pain and depressive symptoms: a cohort study with a 7-year follow-up. *Eur J Pain* 2010;14:189–93
9. Leino P, Magni G: Depressive and distress symptoms as predictors of low back pain, neck-shoulder pain, and other musculoskeletal morbidity: a 10-year follow-up of metal industry employees. *Pain* 1993;53:89–94

10. Kapreli E, Vourazanis E, Strimpakos N: Neck pain causes respiratory dysfunction. *Med Hypotheses* 2008; 70:1009–13

11. Hough A: *Physiotherapy in Respiratory Care: an Evidence-Based Approach to Respiratory and Cardiac Management*, ed 3. Croatia, Cheltenham, UK, Nelson Thornes, 2001

12. Nishino T, Shimoyama N, Ide T, et al: Experimental pain augments experimental dyspnea, but not vice versa in human volunteers. *Anesthesiology* 1999;91: 1633–8

13. Borgbjerg FM, Nielsen K, Franks J: Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. *Pain* 1996;64:123–8

14. Kato Y, Kowalski CJ, Stohler CS: Habituation of the early pain-specific respiratory response in sustained pain. *Pain* 2001;91:57–63

15. Glynn CJ, Lloyd JW, Folkhard S: Ventilatory response to intractable pain. *Pain* 1981;11:201–11

16. McLaughlin L, Goldsmith CH, Coleman K: Breathing evaluation and retraining as an adjunct to manual therapy. *Man Ther* 2011;16:51–2

17. Dimitriadis Z, Kapreli E, Strimpakos N, et al: Respiratory weakness in patients with chronic neck pain. *Man Ther* 2013;18:248–53

18. Price DD, McGrath PA, Rafii A, et al: The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983;17:45–56

19. Wewers ME, Lowe NK: A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health* 1990;13:227–36

20. Carlsson AM: Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. *Pain* 1983;16:87–101

21. Trouli MN, Vernon HT, Kakavelakis KN, et al: Translation of the Neck Disability Index and validation of the Greek version in a sample of neck pain patients. *BMC Musculoskelet Disord* 2008;9

22. Cleland JA, Childs JD, Whitman JM: Psychometric properties of the Neck Disability Index and Numeric Pain Rating Scale in patients with mechanical neck pain. *Arch Phys Med Rehabil* 2008;89:69–74

23. Vernon H, Mior S: The Neck Disability Index: a study of reliability and validity. *J Manipulative Physiol Ther* 1991;14:409–15

24. Baecke JA, Burema J, Frijters JE: A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr* 1982;36:936–42

25. Georgoudis G, Oldham JA: Anxiety and depression as confounding factors in cross-cultural pain research studies: validity and reliability of a Greek version of the Hospital Anxiety and Depression Scale. *Physiotherapy* 2001;87:92–3

26. Georgoudis G, Papathanasiou G, Spiropoulos P, et al: Cognitive assessment of musculoskeletal pain with a newly validated Greek version of the Fear-Avoidance Beliefs Questionnaire (FABQ). *Eur J Pain* 2007;11: 341–51

27. Argyra E, Georgoudis G, Chatzidimitriou A, et al: Cognitive assessment of Greek pain patients: validation of the Pain Catastrophing Scale. *Palliat Med* 2006; 20:232

28. Cleland JA, Fritz JM, Childs JD: Psychometric properties of the Fear-Avoidance Beliefs Questionnaire and Tampa Scale of Kinesiophobia in patients with neck pain. *Am J Phys Med Rehabil* 2008;87:109–17

29. Miro J, Nieto R, Huguet A: The Catalan version of the Pain Catastrophizing Scale: a useful instrument to assess catastrophic thinking in whiplash patients. *J Pain* 2008;9:397–406

30. Bjelland I, Dahl AA, Haug TT, et al: The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52: 69–77

31. Hinkelbein J, Floss F, Denz C, et al: Accuracy and precision of three different methods to determine P_{CO_2} (Pa_{CO_2} *vs.* Pet_{CO_2} vs. $P_{tc}CO_2$) during interhospital ground transport of critically ill and ventilated adults. *J Trauma* 2008;65:10–8

32. Nishiyama T, Kohno Y, Koishi K: Comparison of ear and chest probes in transcutaneous carbon dioxide pressure measurements during general anesthesia in adults. *J Clin Monit Comput* 2011;25:323–8

33. Shapiro BA, Cane RD: Blood gas monitoring: yesterday, today, and tomorrow. *Crit Care Med* 1989;17: 573–81

34. Lee-Chiong T: *Sleep Medicine: Essentials and Review*. New York, Oxford University Press, 2008

35. Kagawa S, Otani N, Kamide M, et al: Initial transcutaneous P_{CO_2} overshoot with ear probe at 42 degrees C. *J Clin Monit Comput* 2004;18:343–5

36. Zuur JK, Muller SH, Sinaasappel M, et al: Influence of heat and moisture exchanger respiratory load on transcutaneous oxygenation in laryngectomized individuals: a randomized crossover study. *Head Neck* 2007;29:1102–10

37. Cuvelier A, Grigoriu B, Molano LC, et al: Limitations of transcutaneous carbon dioxide measurements for assessing long-term mechanical ventilation. *Chest* 2005;127:1744–8

38. Domingo C, Canturri E, Lujan M, et al: Transcutaneous measurement of partial pressure of carbon dioxide and oxygen saturation: validation of the SenTec monitor. *Arch Bronconeumol* 2006; 42:246–51

39. Rodriguez P, Lellouche F, Aboab J, et al: Transcutaneous arterial carbon dioxide pressure monitoring in critically ill adult patients. *Intensive Care Med* 2006;32:309–12

40. Vivien B, Marmion F, Roche S, et al: An evaluation of transcutaneous carbon dioxide partial pressure monitoring during apnea testing in brain-dead patients. *Anesthesiology* 2006;104:701–7

41. Storre JH, Steurer B, Kabitz HJ, et al: Transcutaneous P_{CO_2} monitoring during initiation of noninvasive ventilation. *Chest* 2007;132:1810–6

42. Maniscalco M, Zedda A, Faraone S, et al: Evaluation of a transcutaneous carbon dioxide monitor in severe obesity. *Intensive Care Med* 2008;34:1340–4

43. Boulouffe C, Jamart J, Vanpee D: Evaluation of transcutaneous measures for P_{CO_2} and P_{O_2} in an emergency department. *Eur J Emerg Med* 2006;13:A2

44. Storre JH, Magnet FS, Dreher M, et al: TCM as a replacement for arterial PCO(2) monitoring during nocturnal non-invasive ventilation. *Respir Med* 2011; 105:143–50

45. Raine S, Twomey LT: Head and shoulder posture variations in 160 asymptomatic women and men. *Arch Phys Med Rehabil* 1997;78:1215–23

46. Strimpakos N, Sakellari V, Gioftsos G, et al: Cervical spine ROM measurements: optimizing the testing protocol by using a 3D ultrasound-based motion analysis system. *Cephalalgia* 2005;25:1133–45

47. Strimpakos N, Sakellari V, Gioftsos G, et al: Intratester and intertester reliability of neck isometric dynamometry. *Arch Phys Med Rehabil* 2004;85:1309–16

48. Jull GA, O'Leary SP, Falla DL: Clinical assessment of the deep cervical flexor muscles: the craniocervical flexion test. *J Manipulative Physiol Ther* 2008;31: 525–33

49. Portney LG, Watkins MP: *Foundations of Clinical Research: Applications to Practice*, ed 3. New Jersey, Pearson International Edition, 2009

50. Henry JL, Sessle BJ: Effects of glutamate, substance P and eledoisin-related peptide on solitary tract neurones involved in respiration and respiratory reflexes. *Neuroscience* 1985;14:863–73

51. Chalaye P, Goffaux P, Lafrenaye S, et al: Respiratory effects on experimental heat pain and cardiac activity. *Pain Med* 2009;10:1334–40

52. Sullivan MJ, Thorn B, Haythornthwaite JA, et al: Theoretical perspectives on the relation between catastrophizing and pain. *Clin J Pain* 2001;17:52–64

53. Whelan RF, Young IM: The effect of adrenaline and noradrenaline infusions on respiration in man. *Br J Pharmacol* 1953;8:98–102

54. Henry JP: Mechanisms by which stress can lead to coronary heart disease. *Postgrad Med J* 1986;62:687–93

55. Holt PE, Andrews G: Hyperventilation and anxiety in panic disorder, social phobia, GAD and normal controls. *Behav Res Ther* 1989;27:453–60

56. Innocenti DM: Hyperventilation, in Pryor JA, Webber BA (eds): *Physiotherapy for Respiratory and Cardiac Problems*. London, Churchill Livingstone, 1998, pp 449–61

57. Seaman DR, Cleveland C: Spinal pain syndromes: nociceptive, neuropathic, and psychologic mechanisms. *J Manipulative Physiol Ther* 1999;22:458–72

58. Taylor S, Abramowitz JS, McKay D, et al: Anxious traits and temperaments, in Stein DJ, Hollander E, Rothbaum BO (eds): *Textbook of Anxiety Disorders*, Arlington, American Psychiatric Publishing, 2009, pp 73–86

59. Palastanga N, Field D, Soames R: *Anatomy and Human Movement*, ed 4. Edinburgh, UK, Butterworth Heinemann, 2002

60. Gossman MR, Sahrmann SA, Rose SJ: Review of length-associated changes in muscle. Experimental evidence and clinical implications. *Phys Ther* 1982;62: 1799–808

61. Comerford MJ, Mottram SL: Movement and stability dysfunction—contemporary developments. *Man Ther* 2001;6:15–26

62. Key J, Clift A, Condie F, et al: A model of movement dysfunction provides a classification system guiding diagnosis and therapeutic care in spinal pain and related musculoskeletal syndromes: a paradigm shift—Part 1. *J Bodyw Mov Ther* 2008;12:7–21

63. Kapreli E, Vourazanis E, Billis E, et al: Respiratory dysfunction in chronic neck pain patients. A pilot study. *Cephalalgia* 2009;29:701–10

64. Pass DA, Bolton JR: The respiratory system, in Robinson WF, Huxtable CRR (eds): *Clinopathologic Principles for Veterinary Medicine*, Cambridge, UK, Cambridge University Press, 1988, pp 99–121

65. Nilsen KB, Sand T, Westgaard RH, et al: Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients. *Eur J Pain* 2007;11:743–55

66. Folgering H, Snik A: Hyperventilation syndrome and muscle fatigue. *J Psychosom Res* 1988;32:165–71

67. Natelson BH, Intriligator R, Cherniack NS, et al: Hypocapnia is a biological marker for orthostatic intolerance in some patients with chronic fatigue syndrome. *Dyn Med* 2007;6:2

68. Charron C, Repesse X, Bouferrache K, et al: $Paco_2$ and alveolar dead space are more relevant than Pao_2/Fio_2 ratio in monitoring the respiratory response to prone position in ARDS patients: a physiological study. *Crit Care* 2011;15:R175

69. Laffey JG, Kavanagh BP: Hypocapnia. *N Engl J Med* 2002;347:43–53

70. McLaughlin L: Breathing evaluation and retraining in manual therapy. *J Bodyw Mov Ther* 2009;13: 276–82

71. Dahan A, Yassen A, Bijl H, et al: Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* 2005;94: 825–34

72. Samet P, Fierer EM, Bernstein WH: Effect of salicylates on ventilatory response to inhaled carbon dioxide in normal subjects. *J Appl Physiol* 1960;15: 826–8