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High altitude underground mining. Acclimatization and possible toxicological risks

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ABSTRACT. **Background.** ***Aim of our study was to measure the first responses to hypobaric hypoxia: changes in ventilation minute, heart rate, and hemoglobin saturation which are important parameters involved in the health of mine-workers at high-altitude.***
Material and Methods. ***We develop a study of parameters mentioned on Chilean miners working in an underground mine at high altitude, between 3.070 and 3.656 masl, in an unusual shift system consisting of 12-hour daily work during 4 days, and consecutive 4 resting days. The results obtained at high altitude are contrasted with the corresponding for clerks working at 800 masl.***
Results. ***Either miners who has work less than 6 months at HA as those who are exposed at their workplace to contaminants, as diesel and others, show Hemoglobin Saturation below 90%. Heart Rate increases in response to exposure to acute and/or chronic hypoxia at high altitude. Miners during their resting period at 800 masl or less show an average heart rate lower than clerks no exposed to high altitude. Average Minute Volume of miners at high altitude, on each and every day of the shift, is higher than the mean volume of clerks at 800 masl.***
Conclusions. ***The most of studied miners present acclimatization responses at high altitude in all the studied parameters. The increase in Minute Volume implies a risky condition due to the increase of inhaled toxic inherent to the production process. It appears as an urgency to study the combined effects of hypobaric at high altitude and toxics present at the underground mine.***

Key words: *miners in High altitude, hypobaric hypoxia, unusual work shifts, acclimatization.*

RIASSUNTO. Miniere sotterranee ad alta quota. Acclimatazione e possibili rischi tossicologici.
Contesto. **Lo scopo del nostro studio é stato quello di misurare le prime risposte all'ipossia ipobarica: cambiamenti della ventilazione minuto, della frequenza cardiaca e dell'saturazione della emoglobina, che sono tra i piú importanti parametri di rischio per la salute dei minatori ad alta quota.**
Materiali e Metodi. **Abbiamo condotto uno studio sui parametri menzionati in minatori cileni che lavorano in una miniera in galleria ad alta quota, tra i 3.070**

Introduction

In Chile, the most of the mining extraction is carried out at geographical High Altitude (HA). The 80% of the mining takes place at more than 3.000 masl; besides there are several deposits located at more than 4.000 masl (1). Due to the location of the mines and the requirements of the production processes, unusual shift work is a necessity, since labor is required without interruption. Unusual shifts and high altitude, are clearly risky conditions for these miners. Shift work modality causes various physical, mental, emotional and social distress in workers, the most evident being the alteration of the circadian rhythm. The circadian rhythm is the responsible of synchronizing functions such as sleep and many performances so they might be optimal during the day. If this rhythm is perturbed as a consequence of shift work, several health problems might occur (2). These include sleep disorders, whose morbidity in shift work is significantly greater than that experienced by day workers (3,4). Another risk is cardiovascular disease (5]. Cardiovascular disease morbidity and mortality in shift workers is higher than in non-shift workers, with an incremental risk of 7.1% for every five years of exposure to shift work after the first five years (6). The incidence of obesity and diabetes are also associated with shift work (7,8) and other studies also relate it to the development of prostate cancer (9,10). Some studies suggest that the risk of prostate cancer is 23% higher among shift workers (9). However, the IARC (International Agency for Research on Cancer) classified shift work involving circadian disruptions as probably carcinogenic to humans (Group 2A). It was considered that there is insufficient evidence to classify this working modality as carcinogenic in humans but so it is in experimental animals (11). In addition, shift work is associated with early aging of workers due to the increased need to recover from work and the increased risk of disability (12).

On the other hand, the Chilean miners carry out their work at intermittent HA, that is, they work at HA, and afterwards, when their shift ends, they rest at their homes, generally located in cities that are at most at 800 masl. It is well known that exposure to HA can cause various diseases, such as: acute mountain sickness, pulmonary hypertension, pulmonary edema, cerebral edema (13,14). At

e i 3.656 mslm, sottoposti a turni di lavoro non convenzionali, consistenti in 12 ore di lavoro al giorno per 4 giorni consecutivi, seguiti da 4 giorni di riposo. I risultati ottenuti ad alta quota si mettono in confronto con quelli ottenuti per i dipendenti che lavorano a 800 mslm.
Risultati. **Tanto i minatori che hanno lavorato ad alta quota per meno di 6 mesi quanto coloro esposti in posti di lavoro a contaminanti, quali diesel e altro, evidenziano livelli di saturazione dell'emoglobina inferiori al 90%. La frequenza cardiaca aumenta in risposta all'esposizione all'ipossia acuta e/o cronica ad alta quota. I minatori durante il riposo a 800 mslm, registrano una media della loro frequenza cardiaca inferiore a quella dei dipendenti non esposti alla altitudine. La media del Volume Minuto dei minatori, in ogni singolo giorno del turno, tanto ad alta quota quanto stanti a 800 mslm é sempre superiore alla media del Volume Minuto dei dipendenti che sviluppano le loro funzioni a 800 m.**
Conclusioni. **La maggior parte dei minatori presenta risposte di acclimatazione ad alta quota in tutti i parametri studiati. L'aumento del volume minuto implica una condizione rischiosa dovuta alla maggiore inalazione di tossici propri dei processi di produzione. Appare urgente lo studio degli effetti combinati dell'ipobaria ad alta quota e le sostanze tossiche presenti nella miniera sotterranea.**

Parole chiave: minatori ad alta quota, ipossia ipobarica, turni di lavoro non convenzionali, acclimatazione.

HA, the barometric pressure is reduced and consequently also the partial pressure of oxygen and the inspired pressure of oxygen. The response mechanisms of the human organism to the fall in inspired pressure of oxygen and therefore to hypoxia are: hyperventilation, polycythemia, hypoxic pulmonary vasoconstriction (15), among others. Is called acclimatization to high altitude the set of beneficial changes that occur in the organism in response to hypoxia caused by HA. The most important physiological response in acclimatization is hyperventilation (15). One of the first mechanisms of acclimatization to HA is the increase in minute ventilation in response to hypoxia. It has also been studied that there are changes in heart rate and that the plasma volume decreases to improve the oxygen transport capacity of the blood, which leads to an increase in hematocrit; this occurs during the first 24-48 hours (see Ref. 16 and Refs. Therein). The degree of lung acclimatization is one of the factors that determine the appearance of symptoms of diseases caused by HA. There are different studies about the necessary time acclimatization takes. In the particular case of intermittent exposure to altitude (chronic intermittent hypoxia) of Chilean miners, there are studies that show that for miners who work in shifts of 7 continuous days at high altitude and 7 days of rest at sea level, there is an improvement in their state of acclimatization after 2.5 years of work at HA (17,18).

In this article, we have studied a group of miners who work in the National Copper Corporation of Chile (Codelco[1]) underground mine, Andina Division, between 3.070 and 3.656 masl in an unusual shift system. This shift consists of 12-hour daily work for 4 consecutive days, after which they rest for another 4 days. The 4 days of work are subdivided into 2 day and 2 night shifts. The miners come and go every day of the shift from their houses at sea level, or almost, to the mine at high altitude. The total working-hours for the whole shift is 48 hours.

This article is organized as follows: in section II we present the methodology, in section III we show the results, and in section IV we present the discussion of the results and conclusions.

Material and Methods

The study was made taking 300 miners of an underground mine and 50 clerks (non-miners) of Codelco Andina Chile. The miners do their labors at the underground mine, located between 3070 and 3656 masl, while the Andes clerks perform their duties at 800 masl.

The medical history of all of them was analyzed in order to have only healthy and non-smoking workers in the final samples. As main selection criteria where taken in account males aged between 22 and 60 with low metabolic load, without any chronic or acute respiratory neither hematological or cardiovascular diseases, as well as no consequences of chronic respiratory diseases; no hypertension or obesity diagnosis, no polycythemia, and finally with no obstructive sleep apnea syndrome diagnosis.

The definitive group of healthy and non-smokers miners is composed by 87 workers which carried out their duties between 3070 and 3656 masl and having a work shift called "4x4"; in other words, two 12-hours day shifts and two 12-hours night shifts, followed by 4 resting days. The healthy and non-smokers clerks, located in the city of Los Andes (800 masl), with a usual shift from Monday to Friday during 9 hours at daylight, is composed of 20 employees.

The sampling workers were completely informed of every step and procedure before they gave their formal consent to participate. Codelco Andina Occupational Health Department gave his approval to the experimental protocol to be carry on.

In order to investigate possible compensation and response mechanisms to hypobaric hypoxia at high altitude, the following physiological indicators were measured: hemoglobin oxygen saturation levels (SO_2, expressed in terms of percentage), heart rate (beats per minute) and minute volume (liters), at different altitudes. Minute volume was measured with a Wright / Haloscale Respirometer, and hemoglobin saturation and heart rate were measured with a pulse oximeter, finger oximeter, model RMS-50D. For each physiological indicator were made 3 measurements and the averages were considered as the final data.

[1] Codelco is the biggest producer of copper in the world and it owns the world's largest known copper reserves and sufficient resources for more than 50 years of operation at current production rates.

Each miner working in the underground mine was examined after a 10-15 minute of resting break. Medical checking took place in two different conditions: at high altitude at the mine-health-emergency-center during day work shifts or night work shifts, and at the Codelco Hospital in Los Andes city (800 masl). The examination at the Codelco Hospital was done on two groups of miners: those who were at their days off and others who were on shift at the mine but they went to the Hospital just for these examinations. Following this procedure, the same miner could have been part of more than just one sampling group (see Table I). On the other hand, the Los Andes clerks were examined at 800 masl only once after a resting break of 10-15 minutes. All the exams were performed by a single Codelco nurse previously trained at the "Instituto Nacional del Tórax[2]" in Santiago, Chile. The complete test lasted approximately 30 minutes per worker. The environmental conditions in which the measurements were made were: temperature between 18º and 20ºC, atmospheric pressure in the mine between 546 and 549 mmHg, and in the Hospital in Los Andes approximately 690 mmHg.

In the statistical analyzes, different tests were applied to determine the normality of the data, the arithmetic mean and the standard deviation were calculated for all the indicators. The control group (clerks at Los Andes) was compared with the samples shown in Table I. A confidence level of 95% (C.L. 95%) was used. The tests applied were: Mann-Whitney, Brunner-Munzel, T Independent, Welch's. The python SciPy-library, NumPy-library were used for data analysis.

Results

The effects of altitude on hemoglobin saturation

Hemoglobin saturation was categorized by altitude at workplace. The miner's groups were also divided according work shifts (see Figure 1). Average hemoglobin saturation higher than 95% was observed only at 800 masl, regardless of whether clerks permanently at Los Andes (800 masl) or miners occasionally down at Los Andes (Rest and Work).

The statistical applied tests have shown that there are not significant differences only among those who were measured at 800 masl: between Los Andes vs Work and between Los Andes vs Rest groups as reported in Fig. 1 and Table II.

Furthermore, the hemoglobin saturation (see Fig. 1 and Table II) presents the highest values in miners of Rest group, while the lowest values are founded at the Day 1 shift, which is the first day at high altitude after 4 days of rest. In addition, Los Andes group presents the most homogenous data (smaller CV). On the contrary, the Day 2 group present the most heterogeneous data (highest CV).

The effects of altitude on heart rate

Concerning Heart Rate, the statistical applied tests have shown that only exist significant differences for Los Andes vs Day 1, as reported in Fig. 2 and Table III.

In addition, the heart rate (see Fig. 2 and Table III) presents the highest average at the Day 1 shift, which is the first day at high altitude after 4 days of rest at 800 masl or less. The lowest value corresponds to the Rest group. Furthermore, the Los Andes and Night 1 groups presents the most homogeneous data (lower CV). On the contrary, the Rest group present the most heterogeneous data (highest CV).

When the miners go down to 800 masl, their average heart rate drops more than that of those who do not work exposed to high altitude.

The effects of altitude on minute volume

For the minute volume variable, the statistical applied tests have shown that exist significant differences for all groups of miners compared to Los Andes clerks, as reported in Fig. 3 and Table IV. It is worth to mention, that the mean of minute volume is always higher for miners than clerks at Los Andes (800 masl).

In comparison with clerks, miners present a much higher minute volume while working at the mine at high altitude and when they come down to town at 800 masl.

Table I. *Samples conformation for statistical analysis*

Sample name	Number of elements in the sample (n)	Medical check condition
Los Andes	20 Employees	800 masl / Workdays
Day 1	61 Miners	Hight Altitud / Day 1 / Shift
Day 2	24 Miners	Hight Altitud / Day 2 / Shift
Night 1	38 Miners	Hight Altitud / Night 1 / Shift
Night 2	25 Miners	Hight Altitud / Night 2 / Shift
Work	36 Miners	800 masl / Workdays
Rest	41 Miners	800 masl / Rest Day

[2] The National Thorax Institute is operated by the Government of Chile, through the Ministry of Health. Since 2007, it has been considered a "highly complex self-managed network establishment", which means that it has a technical complexity higher than that of common healthcare centers. It has a multidisciplinary team specialized in the thorax of patients, where transplants are commonly performed and treatments for main heart and respiratory diseases are practiced.

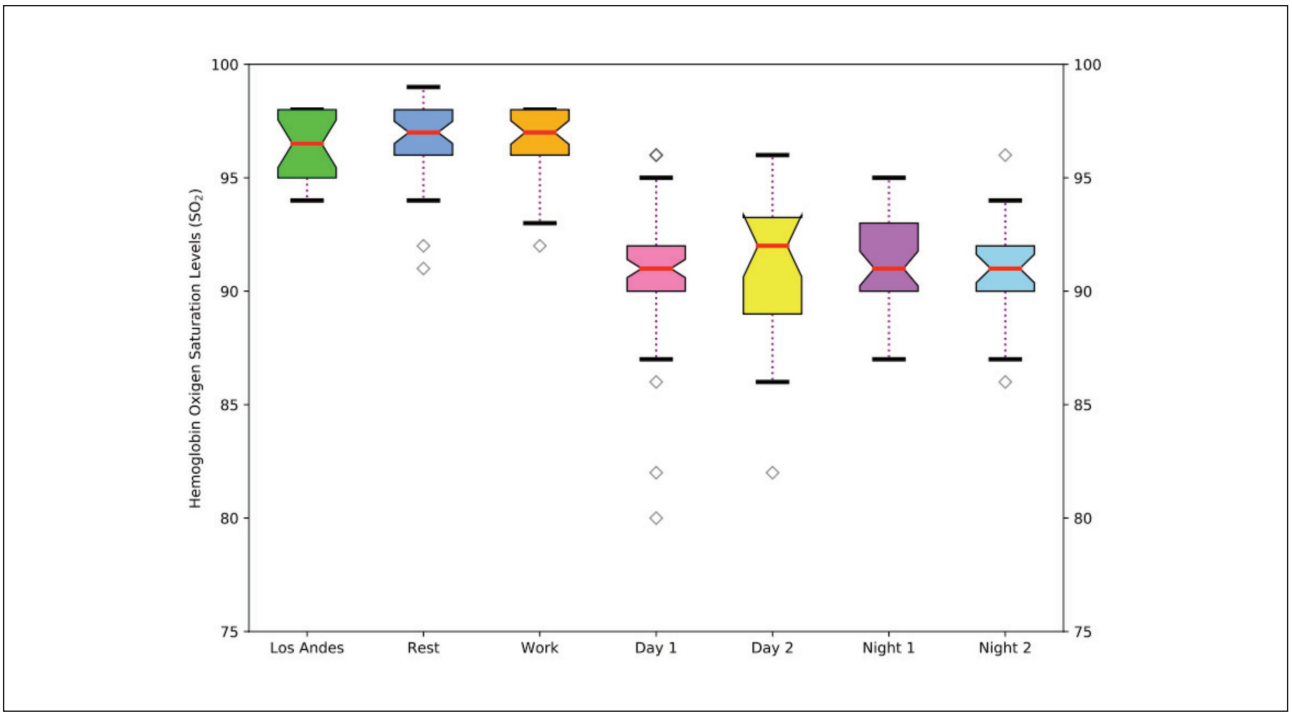

Figure 1. ***Boxplot for the Hemoglobin Saturation (%) for all sampled groups***

Table II. ***Hemoglobin Saturation for all sampled groups. Std dev stand for the standard deviation and CV for the coefficient of variation***

Hemoglobin Saturation (%)			
	Mean	**Std Dev**	**CV**
Los Andes	96,400	1,356	0,014
Rest	96,804	1,863	0,019
Work	96,722	1,464	0,015
Day 1	90,704	2,748	0,030
Day 2	91,041	3,155	0,035
Night 1	91,578	2,208	0,024
Night 2	90,800	2,135	0,024

This means that miners maintain higher minute volume in spite of the altitude where they find themselves.

Furthermore, the minute volume (see Fig. 3 and Table IV) presents the highest average at the Night 2 of the shift, which is the fourth day at high altitude, while the lowest is at Los Andes group (clerks at 800 masl). In addition, Los Andes group presents the most homogenous data (smaller CV).

Discussion

Hemoglobin Saturation

In healthy adults, as in the case of the samples studied, a hemoglobin saturation less than 90% could imply an inadequate supply of oxygen to vital tissues and organs (19), so facilitating the conditions for different diseases to occur. In the sample studied, 32% of the miners when at work at HA either by night shift or in daylight shift saturates less than 90%. On the contrary, in clerks at Los Andes and miners when they go down to Los Andes (800 masl), no values lower than 90% are registered.

Miners with hemoglobin saturation lower than 90% present two interesting characteristics: some have been working at HA for less than 6 months and the others are workers in the same area (level C) and in positions with similar exposure. Is to be concluded that miners working for less than 6 months at HA they still not get acclimated to HA. At least respect to this parameter they don't behave as the ones that are working at HA for 2 years or more. At the area (level C) diesel engines are at work and process are carried on generating different contaminants, among them diesel emissions and crystalline silica. We do not have specific measurements of the chemical contaminants present in this work area. In future studies, it would be important to monitor these workers in order to evaluate the concentration of chemical pollutants in their work area, especially those emitted by internal combustion machinery. An exposure to chemicals that could alter oxygen

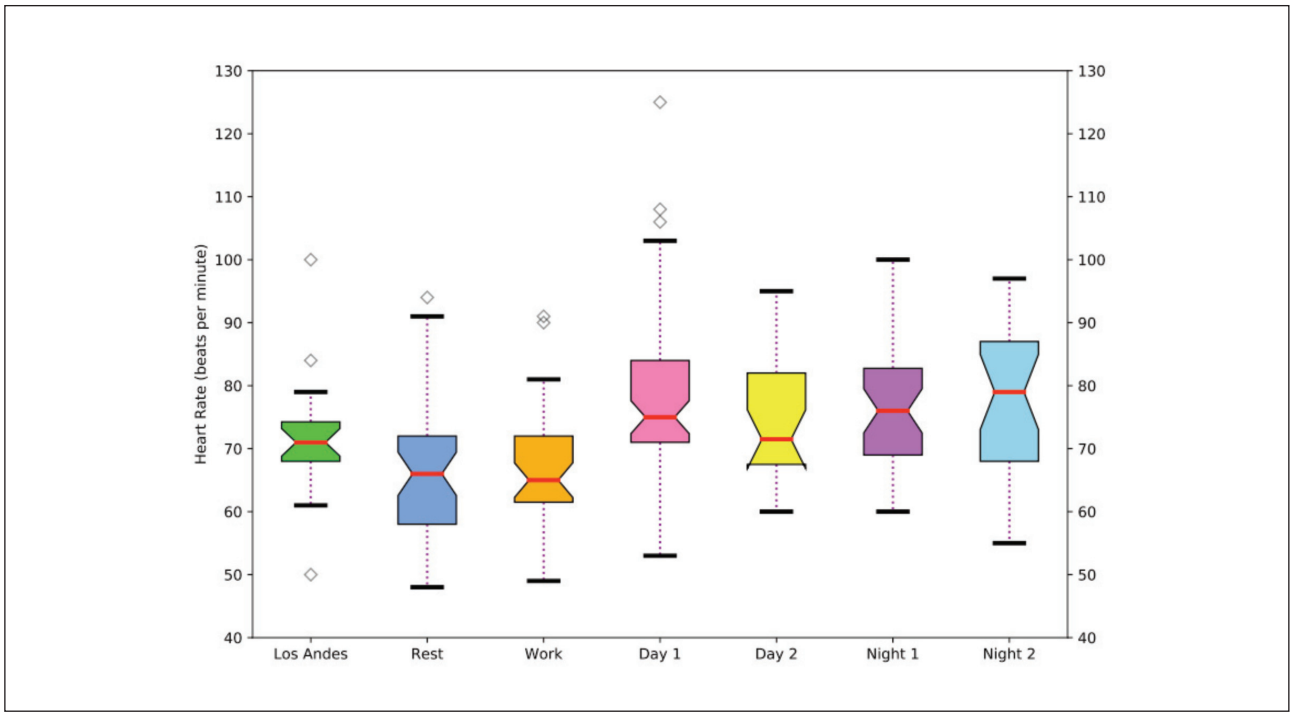

Figure 2. ***Boxplot for the Heart Rate (beats per minute) for all sampled groups***

Table III. ***Heart rate for all sampled groups. Std dev stand for the standard deviation and CV for the coefficient of variation***

Heart Rate (beats per minute)			
	Mean	**Std Dev**	**CV**
Los Andes	71,7	9,6	0,134
Rest	66,7	11,0	0,165
Work	66,8	9,3	0,139
Day 1	78,1	12,7	0,163
Day 2	74,9	10,9	0,146
Night 1	76,2	10,2	0,134
Night 2	76,9	12,3	0,160

saturation is likely to be found in this area. It is urgent to know exactly whether changes in saturation are due only to altitude or also to the presence of some chemical pollutants with asphyxiating characteristics or others.

Some authors maintain that at HA there is an increase in endogenous carboxyhemoglobin even in the absence of inhaled carbon monoxide (20). Due to the characteristics of the mine, ventilation is not the same in all work areas; observations in the field shows that it is necessary to improve ventilation in those areas where the operators with less saturation are found.

When comparing the study groups, it can be seen that there are significant differences in the hemoglobin saturation of the group working at Los Andes (800 masl) compared to group working at high altitude (3070-3600 masl); both in the shift of day and night, and whatever the day of the shift. However, when miners go down to 800 masl, either because they finished the 4 continuous days of the shift and their rest days correspond to them, or because they go to the clinic to take their exams, the hemoglobin saturation behaves again as it does in Los Andes clerks and none of them have a saturation lower than 90%. Therefore, we can conclude that miner's oxygen saturation recovers relatively easily with decreasing altitude. In Fig. 1 it can be observed that the mean saturation of the hemoglobin is significantly higher at 800 masl than at 3000 masl.

In studies of people living in altitude, hemoglobin saturation values are found between 92% and 95% at 3250 masl, and between 90% and 93% at 3600 masl (21). The study clarifies that this data do not apply to non-acclimatized people. In our samples, the vast majority of miners at HA present values in these ranges, so is likely that they present acclimatization characteristics in this parameter.

Heart Rate

Heart rate increases in response to exposure to acute and / or chronic hypoxia at high altitude (22, 23). Our

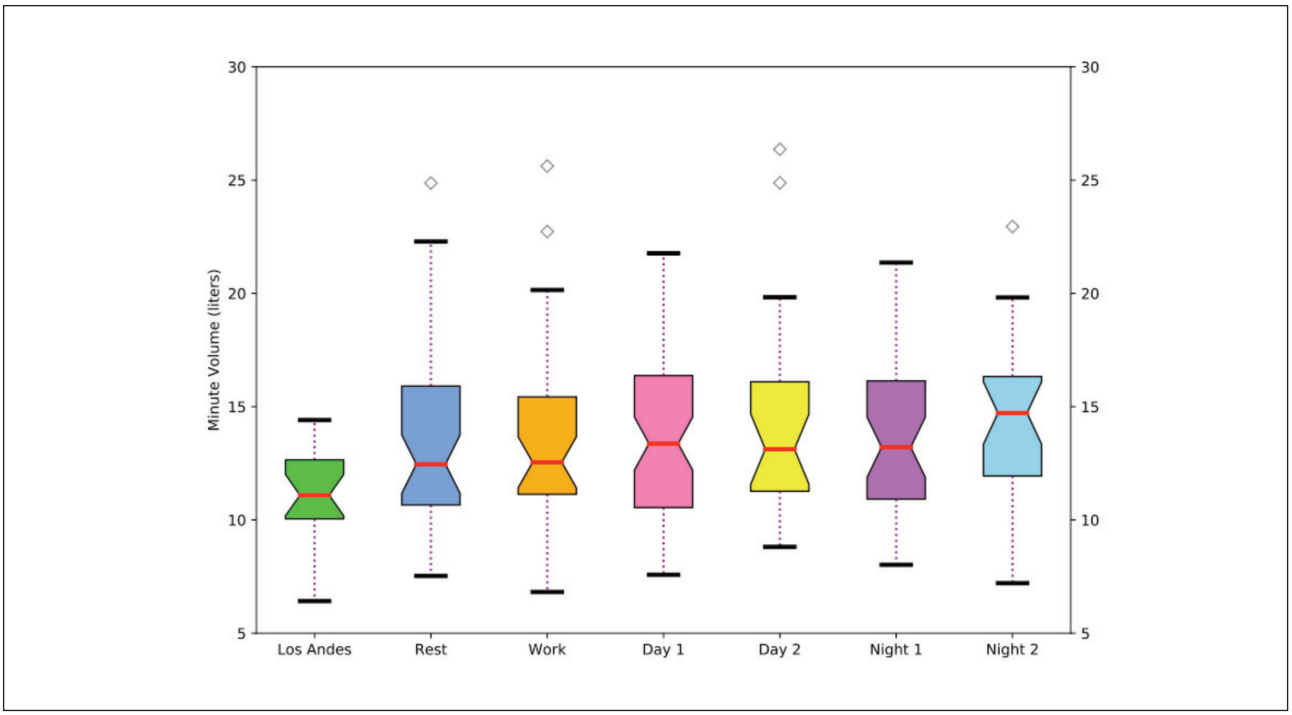

Figure 3. ***Boxplot for the Minute Volume (liters) for all sampled groups***

Table IV. ***Minute Volume for all sampled groups. Std dev stand for the standard deviation and CV for the coefficient of variation***

Minute Volume (liters)			
	Mean	**Std Dev**	**CV**
Los Andes	11,199	2,032	0,181
Rest	13,493	4,094	0,303
Work	13,583	3,961	0,292
Day 1	13,711	3,698	0,270
Day 2	14,257	4,460	0,313
Night 1	13,699	3,400	0,248
Night 2	14,613	3,514	0,240

study confirms that the highest mean heart rate is found in workers who are at HA during all days of their work shift. It is specially significant that when these workers go down to 800 masl, their average heart rate drops more than that of those who do not work exposed to HA, always staying within normal ranges.

An interesting finding emerges when comparing the heart rate of Los Andes clerks with all others groups. Significant differences were found between Los Andes and Day 1 group. It is on the first day of the shift (Day 1) when the highest average heart rate is obtained, while descent in the following shifts. Heart rate increases in the first minutes of exposure to HA and then decreases (24). It is interesting to observe the behavior of the heart rate as a function of working hours during the first day of the shift. In our measurements, the highest frequencies recorded (mean = 95) occurs during the first 4 hours of the morning. In the measurements of the following 8 hours, the average drops to 73. We report that in clinical surveys, miners report that they feel various discomforts on the first day of the shift. We hypothesize that one of the possible causes of these discomforts is that the higher heart rate increases the sensation of fatigue. We consider that it is important to study in depth which and how many other physiological changes are manifested during the first day of ascent at higher altitudes, after 4 days of rest at 800 masl or less.

Minute Volume

Increased pulmonary ventilation is one of the organism's first responses to hypobaric hypoxia caused by high altitude (16). In our study, it can be observed that miners mean minute volume, when they are at high altitude, on each and every day of the shift, is higher than clerk's at Los Andes. Significant differences are found between Los Andes and all other groups. The mean of the minute volume in Los Andes is 11.2, unlike miners, who either on working days at HA or when they go down to

Los Andes have a higher mean of minute volume, between 13.5 and 14.6. We observe that miners, in none of the situations studied, present ventilation values similar to those of clerks at Los Andes (800 masl). We confirm that these miners respond positively to hypoxia with an increase in minute volume. Regarding this last parameter, we emphasize that despite the fact that their work at HA is intermittent, they maintain some acclimatization responses such as hyperventilation even on their rest days.

Increased pulmonary ventilation is one of the most important changes in the acclimatization process (24), which partially compensates hypoxia, which should be considered positive. However, from the point of view of toxic inhalation it is rather alarming. We consider essential to have a special regulation for the permissible limits of chemical contaminants in HA that considers inhaled doses. Most urgent seems the necessity of having an official regulation for diesel emissions and for crystalline silica. There are studies that confirm that at high altitude a higher crystalline silica dose is inhaled (25) and consequently miners who work at HA suffer a prompt development of various pneumoconiosis, among which is silicosis (see Ref. 16 and Refs therein).

On the other hand, it should be taken into consideration that some authors argue that Carbon Monoxide and HA can have additive effects because they are both hypoxia inducers (26). In addition, diesel emissions also contain irritating gases, and therefore is urgent to carry out medical and environmental surveillance in the underground mines located at HA, taking into account the physical (partial pressure of gases) and physiological problems associated with the decrease in the barometric pressure.

About the data variability, we must remark that for all the parameters measured, the most homogeneous data is the one of the Los Andes clerks; miners, instead, are more heterogeneous probably because they present acclimatization responses to HA in different degree according to individual susceptibility. In other words, not all of them go through the acclimatization process in the same way.

Codelco Andina workers have annual controls where a complete medical check-up is carried out, and it is clear that the company shows great concern for the occupational health of its workers. We consider that as part of the medical surveillance, in addition to the annual controls carried out in Los Andes (800 masl), it would be important to implement a program where the physiological parameters analyzed in this study, among other non-invasive parameters, should be measured at high altitude where the mine is located. We emphasize that infrastructure is available since there are permanent medical facilities in the mine. Having hemoglobin saturation measurements by pulse oximetry is not only useful for monitoring oxygen levels, but can also be helpful in the early detection of silicosis in HA miners (27). In addition, having minute volume measurements would allow estimating inhaled doses for different toxic, which would be more appropriate to evaluate the actual exposure to chemical pollutants at high altitude.

Conclusions

The most of studied miners present acclimatization responses at HA in all parameters. These responses are different according to individual susceptibilities and specific workplace conditions. In HA hemoglobin saturation depends on area, job position, and job seniority. The heart rate is higher on day 1 of work in HA after rest. The minute volume is always higher in HA. The increase in Minute Volume implies a risky condition due to the increase of inhaled toxic inherent to the production process.

Acclimatization to altitude in miners implies physiological responses of adaptation that can accelerate the early development of different occupational pathologies exacerbated by the greater inhalation of toxics that occurs at altitude. It appears as an urgency to study the combined effects of hypobaric at high altitude and toxics present at the underground mine.

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Conflict of interest

All authors have no conflicts of interest to declare.

References

1) Departamento de Estudios de la Dirección del Trabajo, Ministerio del Trabajo, Gobierno de Chile. 2011. Una aproximación a las condiciones de trabajo en la gran minería de altura. ISBN: 978-956-7978-11-3.
2) Josephine Arendt, Shift work: coping with the biological clock, Occupational Medicine, Volume 60, Issue 1, January 2010, Pages 10-20, https://doi.org/10.1093/occmed/kqp162
3) Christopher L. Drake, PhD, Timothy Roehrs, PhD, Gary Richardson, MD, et al. Shift Work Sleep Disorder: Prevalence and Consequences Beyond that of Symptomatic Day Workers, Sleep, Volume 27, Issue 8, December 2004, Pages 1453-1462, https://doi.org/10.1093/sleep/27.8.1453
4) Yazdi Z, Sadeghniiat-Haghighi K, Loukzadeh Z, et al. Prevalence of Sleep Disorders and Their Impacts on Occupational Performance: A Comparison between Shift Workers and Nonshift Workers. Sleep Disord. 2014; 2014: 870320. doi: 10.1155/2014/870320. Epub 2014 May 20. PMID: 24977041; PMCID: PMC4055012.
5) Kecklund G, Axelsson J. Health consequences of shift work and insufficient sleep. BMJ. 2016 Nov 1; 355: i5210. doi: 10.1136/bmj.i5210. PMID: 27803010.
6) Torquati L, Mielke GI, et al. Shift work and the risk of cardiovascular disease. A systematic review and meta-analysis including dose response relationship. Scand J Work Environ Health 2018; 44(3): 229-238. doi:10.5271/sjweh.3700.
7) Poulsen K, Cleal B, Clausen T, et al. Work, diabetes and obesity: a seven year follow-up study among Danish health care workers. PLoS One. 2014 Jul 28; 9(7): e103425. doi: 10.1371/journal.pone.0103425. PMID: 25068830; PMCID: PMC4113351.
8) Kanikowska D, Sato M, Witowski J. Contribution of daily and seasonal biorhythms to obesity in humans. Int J Biometeorol. 2015 Apr; 59(4): 377-84. doi: 10.1007/s00484-014-0871-z. Epub 2014 Jul 18. PMID: 25034796; PMCID: PMC4427629.
9) Yong Gan, Liqing Li, Liangwen Zhang, et al. Association between shift work and risk of prostate cancer: a systematic review and meta-

analysis of observational studies, Carcinogenesis, Volume 39, Issue 2, February 2018, Pages 87-97, https://doi.org/10.1093/carcin/bgx129.
10) Salamanca-Fernández E, Rodríguez-Barranco M, Guevara M, et al. Night-shift work and breast and prostate cancer risk: updating the evidence from epidemiological studies. An Sist Sanit Navar. 2018 Aug 29; 41(2): 211-226. English. doi: 10.23938/ASSN.0307. PMID: 30063040.
11) International Agency for Research on Cancer. Volume 124: night shift work. IARC Working Group. Lyon, France; June 4-11, 2019. IARC Monogr Eval Carcinog Risk Chem Hum (in press). DOI: https://doi.org/10.1016/S1470-2045(19)30455-3.
12) Gommans F, Jansen N, Stynen D, et al. The ageing shift worker: a prospective cohort study on need for recovery, disability, and retirement intentions. Scand J Work Environ Health 2015; 41(4): 356-367. doi: 10.5271/sjweh.3497.
13) Escuela de Salud Pública, Universidad de Chile. 2013. Informe Final: Elaboración de un estudio sobre la población trabajadora de faenas mineras en altura geográfica y análisis de riesgos laborales asociados a altitud.
14) Gökhan Aksel, Şeref Kerem Çorbacıoğlu, Can Özen. High-altitude illness: Management approach, Turkish Journal of Emergency Medicine, Volume 19, Issue 4, 2019, Pages 121-126, ISSN 2452-2473, https://doi.org/10.1016/j.tjem.2019.09.002.
15) West John, High-Altitude Medicine, American Journal of respiratory and Critical Care Medicine, (186). https://doi.org/10.1164/rccm.201207-1323CI
16) Vearrier D, Greenberg M. Occupational health of miners at altitude: adverse health effects, toxic exposures, pre-placement screening, acclimatization, and worker surveillance. Clinical Toxicology. https://doi.org/10.3109/15563650.2011.607169.
17) Farias JG, Osorio J, Soto G, et al. Sustained acclimatization in Chilean mine workers subjected to chronic intermittent hypoxia. High Alt Med Biol. 2006 Winter; 7(4): 302-6. doi: 10.1089/ham.2006.7.302. PMID: 17173515.
18) Richalet JP, Donoso MV, Jiménez D, et al. Chilean miners commuting from sea level to 4500 m: a prospective study. High Alt Med Biol. 2002 Summer; 3(2): 159-66. doi: 10.1089/15270290260131894. PMID: 12162860.
19) American Conference of Governmental Industrial Hygienists (ACGIH), 2015. Threshold limit values and biological exposure indices, Cincinnati, USA, Signature Publications.
20) McGrath JJ. Effects of altitude on endogenous carboxyhemoglobin levels. J Toxicol Environ Health. 1992 Feb; 35(2): 127-33. doi: 10.1080/15287399209531601. PMID: 1542134.
21) Rojas-Camayo J, Mejia CR, Callacondo D, et al. Reference values for oxygen saturation from sea level to the highest human habitation in the Andes in acclimatised persons. Thorax. 2018 Aug; 73(8):776-778. doi: 10.1136/thoraxjnl-2017-210598. Epub 2017 Oct 20. PMID: 29054885.
22) Naeije R. Physiological adaptation of the cardiovascular system to high altitude. Prog Cardiovasc Dis. 2010 May-Jun; 52(6): 456-66. doi: 10.1016/j.pcad.2010.03.004. PMID: 20417339.
23) Attias J, Bieles J, Carvil P, et al. Altitude exposure and increased heart rate: the role of the parasympathetic nervous system. J Physiol. 2017, 595: 4589-4590. https://doi.org/10.1113/JP274220
24) Ward M, Milledge J, West J. 2000. High Altitude Medicine and Physiology, London, UK, Arnold.
25) Bacaloni A, Zamora Saà MC, Sinibaldi F, et al. Respiratory parameters at varied altitudes in intermittent mining work. Int J Occup Med Environ Health. 2018 Jan 7; 31(2): 129-138. doi: 10.13075/ijomeh.1896.01082. Epub 2017 Oct 13. PMID: 29035402.
26) McGrath JJ. Carbon monoxide studies at high altitude. Neurosci Biobehav Rev. 1988 Fall-Winter; 12(3-4): 311-4. doi: 10.1016/s0149-7634(88)80064-2. PMID: 3067158.
27) Donroe JA, Maurtua-Neumann PJ, Gilman RH, et al. Surveillance for early silicosis in high altitude miners using pulse oximetry. Int J Occup Environ Health. 2008 Jul-Sep; 14(3): 187-92. doi: 10.1179/oeh.2008.14.3.187. PMID: 18686718.

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