Journal of Biological Engineering Research and Review, 2019; 6(1): 44-48
ISSN: 2349-3232 Online
DOI: 10.5281/zenodo.15356148

Research Article

Effect of acute hypobaric hypoxia on blood pressure and heart rate and its restoration by chlorogenic acid

Alok Ranjan, Alok Prakash, Ranjana Patnaik*

School of Biomedical Engineering, Indian Institute of Technology (Banaras Hindu University), Varanasi, India

***Corresponding author. E-mail: rpatnaik.bme@iitbhu.ac.in (R Patnaik)**

ARTICLE INFO:

Article History:
Received: 23/02/2019
Revised: 22/04/2019
Accepted: 01/05/2019
Available Online: 11/05/2019

Keywords:
Hypobaric; Hypoxia; High-altitude; Chlorogenic acid; Blood pressure; Heart rate

Citation: Ranjan A, Prakash A, Patnaik R. Effect of acute hypobaric hypoxia on blood pressure and heart rate and its restoration by chlorogenic acid. Journal of Biological Engineering Research and Review. 2019, 6(1), 44-48

Abstract: Increase in altitude is always accompanied with low pressure and lack of oxygen. In order to replicate high altitude conditions in normal altitudes, hypobaric hypoxia model is often studied. Chlorogenic acid is known to have a variety of effects on health and is most notably used to reduce blood pressure and weight loss. In the present study, a simple hypobaric condition has been created using a hypobaric chamber in which various pressure points (0.06, 0.05 and 0.04 MPa) has maintained for different time periods (1h, 2h and 4h). The study has been simulated in rat model and their physiological conditions including systolic blood pressure and heart rate was monitored after exposure of hypobaric pressure at different time periods with or without administration of chlorogenic acid. Data reveals that a brief exposure to low pressure do not affect the physiological conditions to a great extent but longer exposures lead to increased blood pressure and heart rate. However, it was observed that pre-treatment with chlorogenic acid enabled the rats to combat the stress and the physiological parameters were reverted near to the normal conditions. It can be concluded from this study that, chlorogenic acid being an antioxidant can help to recover the altered physiological condition induced by hypobaric hypoxia. Further, biochemical studies are required to explore the ameliorating mechanism. The study also provides an idea regarding the physiological changes taking place in rats due to low pressure.

INTRODUCTION

Oxygen is one of the most important components required to maintain human body functions. It is responsible for energy production which is utilized by biological pathways by the oxidation of complex chemical food-stuff. High Altitude is approximately defined as the height between 8,000 feet (2500 m) to 16,000 feet (5000m) above the sea level [1]. According to Dalton's law, the total pressure of air is equal to the sum of partial pressures of gases it contains, so it can be represented as (taking only the major gases):

$P = pO_2 + pCO_2 + pN_2 + pH_2O$ [2]

pH_2O and pCO_2 doesn't depend upon altitude, only pO_2 and pN_2 decrease with an increase in the height. Therefore at high Altitude, low partial pressure of O_2 leads to hypoxia. Above 10,000 feet, the arterial oxygen saturation falls rapidly due to an increased 2,3-diphosphoglycerate concentration in RBCs [3]. It is slightly less than 70% at 20,000 feet and much less at higher altitudes. Low oxygen partial pressure due to hypobaria greatly hinders diffusion, and therefore reduces formation of oxyhemoglobin. Human body is designed specifically in such a manner that it can deliver adequate O_2 to the body tissues only when oxygen is supplied at a pressure close to the sea-level (P = 760 mm Hg) (PO2 =159 mm Hg) [4]. So, at high altitudes low partial pressure of oxygen leads to hypobaric hypoxia which affects the tissue oxygenation and in turn leads to physiological derangements.

Increase in altitude leads to high-altitude sickness, which is showing a higher prevalence in the recent times due to increased number of high altitude travelers especially of South America, Nepal, and India [5]. High altitude sickness is a common name for illnesses that can occur at high altitude, usually above 3000 meters from sea level. Acute or chronic exposure to high altitude causes reduced arterial oxygen saturation resulting an increase in blood hemoglobin levels and pulmonary arterial hypertension [6]. Various types of higher altitude sicknesses have been reported, which include high-altitude cerebral and pulmonary edema and acute mountain sickness [7]. The underlying causative reason behind these altitude dependent diseases remain the same,

lowering of partial pressure of oxygen (PO_2). Reduced PO_2 in high altitude regions leads to development of a condition known as hypobaric hypoxia [8]. Hypobaric hypoxia has always been a keen topic of interest for aviators, space pilots and researchers since it considerably changes the physiological and psychological parameters within few hours. With an increase in the number of people in high altitude zones and attention being shifted to high altitude related physiological and biological problems, more scientific studies are required to understand the symptoms related to these conditions in order to design proper therapeutics.

Chlorogenic acid (CGA) is an ester of caffeic acid and (−)-quinic acid, found in green coffee, vegetables, fruits and tea [9]. Chlorogenic acid is most commonly supplemented in the form of green coffee extract and it is estimated that green coffee beans contain approx. 5–12% [10]. It has a variety of effects on health and is most notably used to reduce blood pressure and weight loss. However, recent studies have indicated that chlorogenic acid may improve mood, reduce oxidative stress, and lower blood sugar levels. It has been postulated that different natural products involving polyphenols such as CGA, resveratrol, and flavonoids have several beneficial effects on health [11]. It has been largely accepted that CGA has several health advantages as an anti-hypertension agent [12]. In another study, it was reported that CGA derived from green coffee extract was the most effective agent in lowering blood pressure and it was also trusty for patients with mild hypertension as well [13]. Results indicated that consuming coffee bean extract could significantly reduce the blood pressure without having any adverse effects. The presence of phenolic compounds, (cynarin and CGA) that are derived from the plant extract, which has a strong vasorelaxant effect may be helpful in the antihypertensive related disorders [14]. On the other hand, results from a meta-analysis also indicated that CGA can significantly ($P \leq 0.05$) reduce both systolic and diastolic blood pressure [15]. Another study demonstrated that CGA can alter the level of nitric oxide and therefore have a relaxing effect on vasodilation of rat vessels [16].

The efficacy of CGA in regulating blood pressure and its role as a vasorelaxant might be further exploited and studied to establish the effect of this phytochemical in combating physiological changes induced by hypobaric hypoxia condition. Hence, this study evaluate the role of CGA in ameliorating the hypobaric-hypoxia induced altered physiological conditions in rat model.

MATERIALS AND METHODS

Animals and Ethical approval

Inbred albino male Charles Foster rats (240 ± 30 g) were used for the study. All the experimental protocols were approved by the Central Animal Ethical Committee at Institute of Medical Sciences, Banaras Hindu University, Varanasi. Standard mice feed and water was available to rats *ad libitum*. All rats was kept under ambient temperature of 25±2°C, with a 12 hour diurnal cycle.

Figure 1: Hypobaric chamber setup and experimental condition

Grouping

The study was aimed at acquiring the physiological parameters (mainly blood pressure and heart rate) under normal, hypoxic and drug treated condition for Charles Foster rats. Rats were randomly divided into three broad groups viz. normal (n=4), hypoxia (n=36) and hypoxia+CGA treated (n=36). The hypoxia group was further subdivided into three groups based on altitude i.e. high altitude (3500 m ≈ 0.06MPa pressure), very high altitude (5500 m ≈ 0.05MPa pressure) and extreme altitude (7500 m ≈ 0.04MPa pressure) were selected for the present study. Each altitude group was further divided into three groups based on exposure time of 1h, 2h and 4h. Similar grouping system was adopted for the treated animals.

Hypobaric Chamber

Hypobaric hypoxia (HH) was induced in a vacuum desiccator 20L (ABDOS Labtech Private Limited, India) equipped with a vacuum pump and pressure gauge (Fig.1). The hypobaric chamber was maintained at ambient air temperature of 28°C and humidity 55%. Rats of each group was placed in the chamber to simulated altitude of 3500, 5500 and 7500 meter for different time periods.

Chlorogenic acid administration

10mg/kg dose of CGA was administered through intranasal route of all treated animal before subjecting to hypoxic condition. The CGA of 80 µl/kg dose volume was prepared in 0.1 M phosphate buffer (PB; pH 7.4) and immediately used for the intranasal dosing.

Systolic blood pressure and Heart Rate measurement

The systolic blood pressure (SBP) and hear rate (HR) of the animals were monitored by the tail cuff method using the NIBP (AD instruments) controller. All awaked rats of each group was kept in a restrainer and the SBP and HR were measured using the non-invasive blood pressure monitor equipped with pulse transducer and tail cuff (Fig. 2). The parameters are noted from the Lab Chart software (Fig. 2).

Statistical analysis

All data were statistically analyzed with GraphPad Prism software and expressed as Mean±S.D. Two way ANOVA was applied to the datasets with Bonferroni posttests and $p<0.05$ were considered statistically significant.

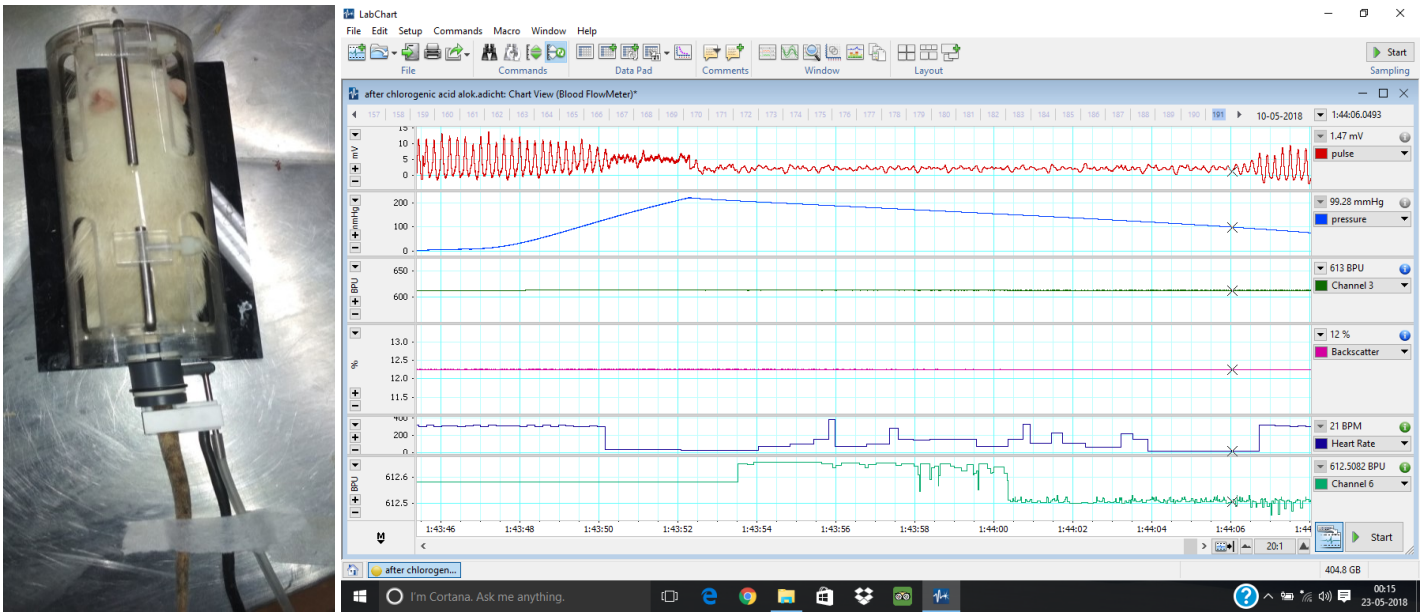

Figure 2: Measurement of SBP, HR by the tail-cuff method and values obtained using Lab Chart Software

RESULTS AND DISCUSSION

The SBP and HR of normal rat group were found 103±3.2 and 254±3.8 respectively. The SBP and HR of hypoxia and hypoxia+CGA treated groups were also recorded and are presented in the tables. An increase in both SBP and HR was observed increase in altitude and exposure time. The highest increase `of SBP and HR was observed during the maximum time of exposure (4 hours) in case of all three altitudes. At 0.06MPa pressure, equivalent to 3500m, an exposure for 4 hours increased the SBP by 26.21% and heart rate by 11.8% as compared to the normal group (Table 1). At 5500m and 7500m, SBP increases by 41.74% and 52.42% respectively, whereas HR increases by 52.36% and 70.47% respectively (Table 2, 3). It was also observed that animals receiving pre-treatment with CGA exhibited lower SBP and HR as compared to the untreated group, though the parameters remained higher than the control group. There was no significant lowering of SBP in the CGA pre-treated animals of high altitude (1h exposure) group, but HR was significantly decreased ($p<0.05$)as compared to the untreated animals exposed to similar conditions. But, significant lowering of the

SBP was observed in CGA treated animals of high altitude groups receiving 2h and 4h exposure ($p < 0.05$ and $p < 0.01$, respectively) along with significantly decreased HR ($p < 0.001$) in comparison to CGA non-treated group. CGA pretreatment also significantly lowered SBP and HR ($p < 0.05$ and $p < 0.001$ respectively) in higher altitude group animals as compared to only hypoxia group after 1h exposure. Both the parameters were also significantly reduced due to CGA pre-treatment ($p< 0.001$) after 2h and 4h exposure in the higher altitude group animals in comparison to animals without CGA pre-treatment. CGA pre-treatment also had similar effect on animals of extreme altitude group since both the physiological parameters (SBP and HR) are significantly reduced ($p < 0.001$) during all the exposure times (1, 2 and 4h) as compared to the CGA non-treated animals exposed to hypoxia for similar time duration. The obtained results thus signify that CGA have an ameliorating effect on the altered physiological conditions induced by hypobaric hypoxia.

Table. 1 Effect of hypobaric hypoxia and pre-administration of CGA on SBP and HR at high altitude (3500 m ≈ 0.06MPa pressure)

Time (h)	SBP		P	HR		P
	Hypoxia	Hypoxia + CGA Treatment		Hypoxia	Hypoxia + CGA Treatment	
1h	109±3.52	106±3.85	P>0.05	267±2.37	261±1.88	P<0.05
2h	123±3.81	115±4.17	P<0.05	326±3.33	276±2.35	P<0.001
4h	130±4.35	118±4.42	P<0.01	354±3.65	284±2.52	P<0.001

Table. 2 Effect of hypobaric hypoxia and pre-administration of CGA on SBP and HR at very high altitude (5500 m ≈ 0.05MPa pressure)

Time (h)	SBP		P	HR		P
	Hypoxia	Hypoxia + CGA Treatment		Hypoxia	Hypoxia + CGA Treatment	
1h	123±3.51	114±3.26	P<0.05	328±3.17	271±3.26	P<0.001
2h	139±4.42	121±3.45	P<0.001	369±3.87	324±3.44	P<0.001
4h	146±4.68	126±4.22	P<0.001	387±4.53	348±3.71	P<0.001

Table. 3 Effect of hypobaric hypoxia after pre-administration of CGA on SBP and HR at extreme altitude (7500 m ≈ 0.04MPa pressure)

Time (h)	SBP		P	HR		P
	Hypoxia	Hypoxia + CGA Treatment		Hypoxia	Hypoxia + CGA Treatment	
1h	140±4.15	125±2.29	P<0.001	364±3.77	332±3.26	P<0.001
2h	153±4.33	129±2.34	P<0.001	410±4.89	351±3.55	P<0.001
4h	157±4.87	136±2.37	P<0.001	433±5.54	363±3.78	P<0.001

CONCLUSION

The physiological parameters investigated during this study were the blood pressure & heart rate. It was observed that both of these parameters increased with the decrease in pressure. With the gradual decrease of pressure in the vacuum chamber, there was an increase in blood pressure of rats as compared to the normal rats. Also, the blood pressure & heart rate is also dependent on the exposure time. These observations can lead to the conclusion that prolonged exposure to low pressure conditions can lead to pathophysiological changes. To combat the physiological changes caused by low pressure, chlorogenic acid was administered to the rats. Cholorogenic acid is an antioxidant and a well-established neuroprotectant. Intra-nasal administration of chlorogenic acid in rats showed improved blood pressure and heart rate conditions. Even after the highest time exposure to the lowest pressure, Chlorogenic acid treated rats showed significantly improved blood pressure and heart rate conditions. This might be due to the fact that chlorogenic acid is and anti-oxidant and successfully scavenges the free radicals generated due to prolonged hypoxia exposure. Therefore, this study gives an idea about the conditions harmful towards physiological conditions and also identifies Chlorogenic acid as a possible treatment for hypobaric hypoxia. To understand the mechanism of Chlorogenic acid's action in ameliorating hypobaric hypoxic conditions, further biochemical studies are being carried out.

REFERENCES

1. Curtis R. OA Guide to High Altitude: Acclimatization and Illnesses. Princeton University. 1999.
2. Cairo JM. Respiratory Care Anatomy and Physiology: Foundations for Clinical Practice. Will D Beachey PhD RRT. St Louis: Mosby Elsevier. 2007. Soft cover, 313 illustrations, color, 448 pages, $58.95.

3. Hackett PH, Roach RC. High-altitude illness. New England journal of medicine. 2001 Jul 12;345(2):107-14.
4. Ortiz-Prado E, Dunn JF, Vasconez J, Castillo D, Viscor G. Partial pressure of oxygen in the human body: a general review. American journal of blood research. 2019;9(1):1.
5. Peacock, A J. ABC of oxygen: oxygen at high altitude. BMJ (Clinical research ed.) vol. 317,7165, 1998: 1063-6. doi:10.1136/bmj.317.7165.1063
6. Bartsch P, Gibbs JS. Effect of altitude on the heart and the lungs. Circulation. 2007 Nov 6;116(19):2191-202
7. Paralikar SJ. High altitude pulmonary edema-clinical features, pathophysiology, prevention and treatment. Indian journal of occupational and environmental medicine. 2012 May;16(2):59
8. Taylor AT. High-altitude illnesses: physiology, risk factors, prevention, and treatment. Rambam Maimonides medical journal. 2011 Jan;2(1)
9. Kumar G, Paliwal P, Mukherjee S, Patnaik N, Krishnamurthy S, Patnaik R. Pharmacokinetics and brain penetration study of chlorogenic acid in rats. Xenobiotica. 2019 Mar 4;49(3):339-45.
10. Kumar, G., Mukherjee, S., Paliwal, P. et al. Naunyn-Schmiedeberg's Arch Pharmacol (2019). https://doi.org/10.1007/s00210-019-01670-x
11. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. Journal of nutritional science. 2016;5.
12. Suzuki A, Kagawa D, Ochiai R, Tokimitsu I, Saito I. Green coffee bean extract and its metabolites have a hypotensive effect in spontaneously hypertensive rats. Hypertension Research. 2002;25(1):99-107.
13. Wan CW, Wong CN, Pin WK, Wong MH, Kwok CY, Chan RY, Yu PH, Chan SW. Chlorogenic acid exhibits cholesterol lowering and fatty liver attenuating properties by up-regulating the gene expression of PPAR-α in hypercholesterolemic rats induced with a high-cholesterol diet. Phytotherapy Research. 2013 Apr;27(4):545-51.
14. Hakkou Z, Maciuk A, Leblais V, Bouanani NE, Mekhfi H, Bnouham M, Aziz M, Ziyyat A, Rauf A, Hadda TB, Shaheen U. Antihypertensive and vasodilator effects of methanolic extract of Inula viscosa: Biological evaluation and POM analysis of cynarin, chlorogenic acid as potential hypertensive. Biomedicine & Pharmacotherapy. 2017 Sep 1;93:62-9.
15. Onakpoya IJ, Spencer EA, Thompson MJ, Heneghan CJ. The effect of chlorogenic acid on blood pressure: a systematic review and meta-analysis of randomized clinical trials. Journal of Human Hypertension. 2015 Feb;29(2):77.
16. Tom EN, Girard-Thernier C, Demougeot C. The Janus face of chlorogenic acid on vascular reactivity: A study on rat isolated vessels. Phytomedicine. 2016 Sep 15;23(10):1037-42.

About Author

Mr. Alok Ranjan has completed his Integrated Dual Degree in Biomedical Engineering from School of Biomedical Engineering, Indian Institute of Technology (Banaras Hindu University), Varanasi. His area of interest are hypobaric hypoxia, electrophysiological signal analysis and bioinstrumentation.