IX

PHYSIOLOGY OF INTERMITTENT EXPOSURE TO HIGH ALTITUDE

ERYTROPOIETIN AND CENTRAL VENOUS PRESSURE IN HIGH ALTITUDE SHIFT WORKERS

Hanns-Christian Gunga, Lothar Röcker, Claus Behn, Wulf Hildebrandt,Eberhard Koralewski, Wolfgang Schobersberger And Karl Kirsch

Freie Universität Berlin, Physiologisches Institut, Amimallee 22, 14 195 Berlin, Germany Departamento de Fisiología y Biofisíca, Facultad de Medicina, Universidad de Chile, Santiago, Chile; Institut für Sport- und Leistungsmedizin, Hospitalstrabe 3, 69115 Heidelberg, Germany; Universitätsklinik für Anästhesie und Allgemeine Intensivmedizin, Anichstrasse 35, 6020 Innsbruck. Austria

RESUMEN: Eritropoyetina y Presión Venosa Central en Trabajadores de Altura Por Turnos

Se planteó la hipótesis que en trabajadores por turnos expuestos a hipoxia intermitente (10 días de trabajo a más de 3,600 m, seguidos de 4 días de descanso a nivel del mar) por más de 5 años, las respuestas de eritropoyetina (EPO) y los cambios en la presión venosa central (CVP) son diferentes de las que se observan en caucásicos que viven a nivel del mar. dado que el compartimiento intersticial pertenece al sistema de baja presión, un objetivo adicional del estudio fue cuantificar los cambios de distribución de líquido en los tejidos superficiales a lo largo del eje corporal durante tal hipoxia intermitente. Se usó un ultrasonógrafo para medir los cambios de espesor tisular de la cabeza (frente) y la tibia en trabajadores de turnos y en caucásicos de nivel del mar. Además se analizaron muestras sanguíneas para medir presión coloido-osmótica (COP) y concentraciones de albúmina (ALB) con la finalidad de determinar si el pasaje de líquido del compartimiento intravascular al extravascular se debe a variaciones de la COP o de la concentración de ALB. Se estudió a personal de cocina (N=11) de la mina de oro La Coipa (3600 m) y a un grupo de caucásicos de nivel del mar (N=5). Se tomó muestras de sangre y se realizó varias mediciones de CVP y densidad tisular (TT) antes, durante y luego de un turno típico. En las muestras basales (BDC) antes del cambio, los trabajadores por turnos presentaron concentraciones de EPO de 5.2±2.4 $mU.ml^{-1}$, que aumentaron en altura ($P<0.01$) y retornaron a valores BDC durante la recuperación (día 16). Los caucásicos mostraron la misma evolución en el tiempo. Los valores CVP en los trabajadores por turnos fueron generalmente superiores a los valores de los caucásicos. La densidad tisular de la región frontal en los primeros aumentó de manera definitiva durante la exposición a la altura ($P<0.05$) y se mantuvo a un nivel elevado durante el período de recuperación ($P<0.05$). la densidad tisular en la tibia no mostró cambios significativos; cambios similares se observaron en los caucásicos de nivel del mar. En conclusión, refutamos la hipótesis según la cual la respuesta inicial de EPO al estímulo hipóxico está alterada en los trabajadores en cuestión. Las más altas concentraciones de hemoglobina y/o de CVP halladas en los trabajadores por turnos podrían explicar las concentraciones más bien bajas de EPO observadas en la BDC. Además, los trabajadores por turnos y los caucásicos de nivel del mar mostraron acumulaciones medibles de líquidos en el tejido superficial de la parte superior del cuerpo, luego del cambio de nivel del mar a la altura.

Palabras claves: Salud, Mineros, Hipoxia intermitente, Presión venosa central, Densidad tisular, Ultrasonido.

RÉSUMÉ: Erythropoïétine et pression veineuse centrale chez les personnes travaillant en altitude et par roulement.

Une hypothèse a été émise selon laquelle, chez les personnes travaillant par roulement et qui ont été exposées de façon intermittente à l'altitude (10 jours de travail à plus de 3 600 m, suivis de 4 jours de repos au niveau de la mer) pendant plus de 5 ans, les réponses de l'érythropoïétine (EPO) et les variations de la pression veineuse centrale (CVP) sont différentes de celles des caucasiens vivant au niveau de la mer. Etant donné que le compartiment interstitiel appartient au système de basse pression, un objectif supplémentaire de l'étude a été de quantifier les changements de distribution de fluide dans les tissus superficiels tout au long de l'axe corporel, au cours du stress hypoxique intermittent. A l'aide d'un appareil à ultrasons on a donc mesuré les changements de densité tissulaire dans la tête (front) et le tibia des travailleurs par roulement et des caucasiens du niveau de la mer. Des prélèvements de sang ont en outre permis de mesurer la pression colloïdo-osmotique (COP) et la concentration d'albumine (ALB), dans le but de déterminer si le passage des fluides du compartiment intravasculaire au compartiment extravasculaire est dû à des variations de la COP et des concentrations d'ALB. L'étude a été faite sur le personnel des cuisines (N=11) de la mine d'or de La Coipa (3 600 m) et sur un groupe de caucasiens du niveau de la mer (N=5). On a effectué des prélèvements de sang et on a mesuré à plusieurs reprises la CVP et la densité tissulaire (TT), avant, pendant et après un roulement normal d'équipes. Dans la collection de base de données (BDC), avant la transition, les travailleurs par équipes présentaient des concentrations d'EPO de 5.2±2.4 $mU \cdot ml^{-1}$ qui augmentèrent en altitude ($P<0.01$) et redescendirent à des valeurs BDC pendant la récupération (le 16e jour). Les caucasiens montrèrent la même évolution dans le temps. Les valeurs CVP chez les travailleurs des équipes de roulement furent généralement supérieures à celles des caucasiens. La densité tissulaire de la région frontale chez les premiers augmenta de façon significative pendant l'exposition à l'altitude (p<0.05) et se maintint à un niveau élevé pendant la période de récupération (p<0.05). La densité tissulaire dans les tibias n'a pas montré de changements significatifs; des changements similaires ont pu être observés chez les caucasiens du niveau de la mer. En conclusion, nous réfutons l'hypothèse selon laquelle la réponse initiale d'EPO au stimulus hypoxique est altérée chez les travailleurs en question. Les plus hautes concentrations d'hémoglobine et/ou de CVP trouvées chez les travailleurs des équipes de roulement pourraient être responsables des concentrations plutôt basses d'EPO observées dans la BDC. En outre, les travailleurs des équipes de roulement et les caucasiens du bord de mer montrèrent des accumulations mesurables de fluides dans le tissu superficiel de la partie supérieure du corps, après passage du niveau de la mer à l'altitude.

Mots-clés : Santé des travailleurs, Hypoxie intermittente, Pression veineuse centrale, Densité tissulaire, Ultrasons.

SUMMARY: It was the hypothesis that in shift workers with a history of intermittent hypoxic stress (working 10 days at >3,600 m, then 4 days rest at sea-level) for >5 years the initial erythropoietin (EPO) response, and the changes in central venous pressure (CVP) are different from Caucasian low-landers. Because the interstitial compartment belongs to the low pressure system, it was an additional aim of the study to quantify fluid distribution changes in the superficial tissues along the body axis during such an intermittent hypoxic stress. Therefore, an ultrasound device was used to measure the tissue thickness changes at the head (front) and tibia in shift workers and Caucasian low-landers. In addition, blood samples were analysed for colloid osmotic pressure (COP) and albumin (ALB) concentrations to evaluate whether fluid shifts from the intravascuiar to the extravascular compartment are probably due to changes in COP and ALB concentrations. We studied the kitchen personnel (N=11) of the goldmine La Coipa (3,600 m) and a group of Caucasian low-landers (N=5). Blood samples were taken and CVP and tissue thickness TT determined several times before, during, and after a typicai shift. At baseline data collection (BDC) prior to transition the shift workers had EPO concentrations of 5.2 + 2.4 mU-ml-1, which increased at altitude (P<0.01) and returned to BDC values on the recovery (day 16). The Caucasians showed the same time course. CVP values in the shift workers were generally higher than in the Caucasians. The tissue thickness at the front in shift workers increased significantly at altitude exposure (P<0.05) and remained elevated in the recovery period altitude (P<0.05). The tissue thickness at the tibia showed no significant changes. Similar tissue thickness changes could be observed in the Caucasian low-landers. In conclusion, the hypothesis has to be refuted that the initial EPO response to a hypoxic stimulus is aitered in these shift workers. Higher hemoglobin concentrations and/or CVP values found in shift workers might be responsible for the rather low EPO concentrations observed in shift workers at BDC. Furthermore, shift workers and Caucasian low-landers showed measurable fluid accumulations in the superficial tissue of the upper part of the body after transition from sea-level to high altitude.

Key words: Occupational Health, Intermittent Hypoxic Stress, Central Venous Pressure, Tissue Thickness, Ultrasound Method

INTRODUCTION

Generally, the mines in the South American Andes are among the highest in the world. Today there is increasing mining activity at altitudes between 3,000 and 6,000 m. In previous times, usually long-adapted local people were recruited for mining at altitudes above 3,000 m. Growing economic interest especially in Peru, Bolivia, and Chile for copper, gold, and silver led to plans to expand exploration and exploitation of these natural resources in the Andes (Monge et al. 1990). It is easy to conceive that the increasing number and the growing size of these mines such as Minera Doña Inés de Collahuasi (Chile) with a population of about 20,000 cannot be run by local personnel only and that people had to be recruited from all over the country. Thus, people from low altitudes (sea-level) were recruited. It is apparent that new physiological, medical, and/or psychological problems related to the establishment of these mines could be predicted, but only scanty information is available on how workers tolerate the high altitude exposure (Jalil 1995; Jimenez 1995; Ward et al. 1995). La Coipa (3,600 - 4,000 m) in the southern Atacama desert of Chile is one of these new mines. Nowadays about 600 people are working permanently in what is one of the richest goldmines in the world. Personnel are recruited from all parts of the country especially from the coastal areas of Chile.

For our study we have chosen the kitchen personnel of the surface-mine La Coipa (location of the study, see figure 1). The reason for choosing this group was to avoid factors which might influence the erythropoietic system by environmental pollution, as is known from Andean underground-mines (Frisancho 1988). The workers usually had continued for more than 5 years a shift of 10 working-days at 3,600 - 4,000 m and a four day rest period at sea level. The mining management determined this schedule, which was most likely tolerated by most of the miners (personal communication). A scientific evaluation on the occupationai health problem still needs to be performed.

It was the hypothesis that in these shift workers the initial erythropoietin (EPO) response and the central venous pressures (CVP) are different from a control group of Caucasian low-landers, who prior to the study had not been exposed to altitudes >3,000 m during the previous six months before the expedition. CVP measurements were included in this study, since previous experimental data in dogs have shown that changes in CVP modulate.

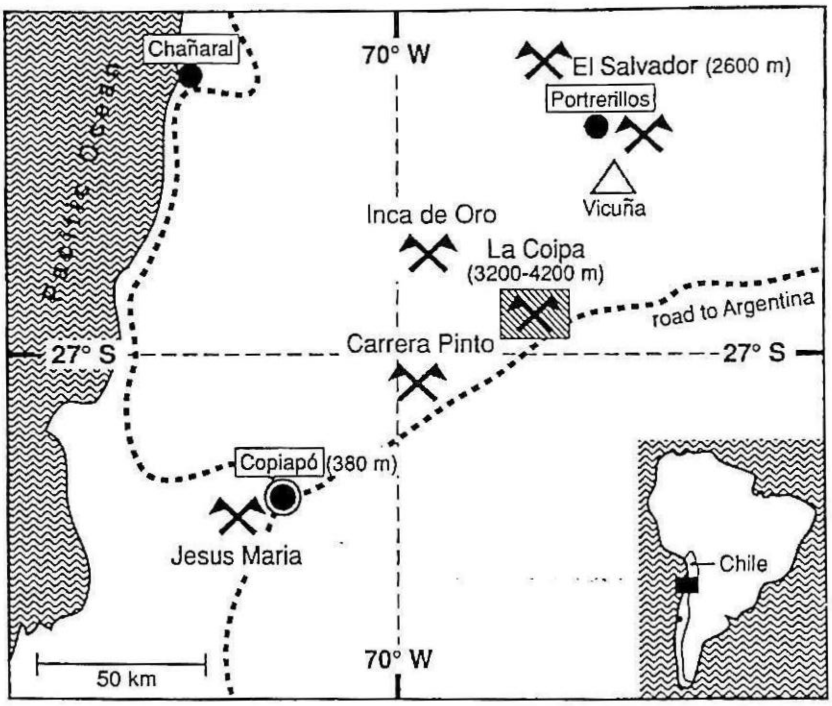

Figure 1. Location of the goldmine La Coipa (3200-4200 m) in Chile. (Map modified after Sylvester and Palacios 1991).

EPO production and release from the kidneys (Ehmke et al. 1995; Just et al. 1993), and similar considerations have been made for man (Gunga et al. 1994). Furthermore, it was assumed that in both group tissue thickness changes at the front (head) and tibia might occur at high altitude, which are known to be present already at moderate altitude exposure (Gunga et al. 1995).

MATERIAL AND METHODS

Location of the study. The study was performed in the southern Atacama desert of the Chilean Andes during April 1994. The baseline data collection (BDC) was taken in Copiap= (380 m, Chile) prior to transition to La Coipa, a new gold mine at an altitude of 3,600 - 4,000 m. The mine is a four-hour drive by car from Copiapó.

Subjects and Protocol. The shift workers (N=11, male, age 34 + 10.3 years, height 1.67 + 0.04 m, body mass 67.0 + 10.3 kg) were working as kitchen personnel in La Coipa. One Chilean shift worker was withdrawn from the study during the first BDC due to several vasovagal syncopies during the blood withdrawal procedure.

The shift workers usually had a shift of 10 days at high altitude in La Coipa and a four day rest period at sea-level. During daytime they were working in the mine between 3600 and 4000 m and slept overnight in a camp at a lower level (3000 m). EPO, reticulocytes, hematocrit, hemoglobin, plasma volume and tissue thickness changes (Δ%) were determined in the shift workers during and after transition to high altitude. The percentag changes in plasma volume (Δ% plasma volume) were calculated from hemoglobin concentrations and hematocrit using standard methods (Strauss et al. 1951). Blood samples from the shift workers were taken on the 1st (=BDC), 6th, 11th, and 16th day during the expedition.

Parallel to the Chilean shift workers, a control group of Caucasian low-landers (N=5, male, age 40.8 + 5.5 years, height 1.84 + 0.09 m, body mass 82.5 + 5.8 kg) was studied. During daytime they were working between 3600 and 4000 m and slept overnight in the same camp of the shift workers at a lower altitude level (3000 m). Blood samples from the Caucasian control group were taken on the 2nd (=BDC), 5th, 7th, 11th, 13th, and 15th day of the study. In addition, EPO values from the shift workers were compared with data obtained by us from a larger group of male Caucasiens (N=49, age 20-50 years).

CVP and ultrasound equipment. The equipment to measure CVP consisted of a small conventional strain gauge connected to a 19-gauge needle, a preamplifier, a small oscilloscope, and a tape recorder to store the signals. This equipment was used during earlier space flights for measuring

CVP under micro-gravity conditions (Kirsch et al. 1984). Pulse-coded modulation was used for data acquisition. CVP was measured by the arm-down method according to Gauer and Sieker (Gauer and Sieker 1956) in 6 out of the 11 shift workers and in all 5 Caucasian control subjects. The CVP measurements were taken at several locations (Caucasians: 3th, 5th, 8th, 11th, and 13th day; shift workers: 4th, =th, 11th, and 16th day of the expedition). Every measurement was made in the morning between 10 a.m. and 12 noon, after the subjects had rested in a supine position for 15 min.

For the tissue thickness measurements an ultrasonic pulse echo equipment was used (CL3DL Kräutkramer and Co, Cologne, FRG). The CL3DL operated on 10 Mhz (Kirsch et al. 1980a; Kirsch et al. 1980b), an equipment which was used sucessfully during space flights (Kirsch et al. 1993), clinical (Gunga et al. 1994) and other field studies (Gunga et al. 1995). The probe (0 = 1.0 cm) transmitts a brief burst of ultrasonic energy that propagates through different materials and is received by the same probe (A-mode). The probes were connected with the instrument by means of a flexible cable. The probe was fitted into a teflon ring which stabilized the system. The weight of the probe and the teflon ring together was 6.5 g. The coupling of the equipment with the tissues induced a deformation from an undisturbed level by less than 2 % assuming a tissue thickness between 2-8 mm. This was experimentally tested. The data could be read directly from a display. Since the values depend on many physiological variables an in situ analysis of the error is mandatory. In order to determine the error of the method in 4 subjects 10 measurements in one location were done within one hour. This gave an standard deviation of 0.04 mm (1 %) for the mean values. The resolution of the ultrasound sensor is 0.5 % of the values obtained in subjects assuming an average tissue thickness of 4.0 mm.

Analytical methods. The blood was centrifuged, and serum was stored immediately at -30°C until tested. EPO was measured by an ELISA distributed by IBL (Hamburg, Germany) with an intra-assay coefficient of variation of 4.8 %. All samples were assayed together in duplicate. The COP was measured with the BMT-921-onkometert® (Thomae, FRG) and the CV in one run was 0.44 %. The hemoglobin (HB) concentrations were measured with a Reflotron® by Boehringer (Mannheim, FRG) (CV 2.0 %), the packed cell volume (PCV) with a micro-packed cell volume centrifuge by Compur®-Electronic (München, FRG) (CV 0.8 %). The percentage changes in PV (delta % PV) were calculated from control and post ascent HB and PCV measurements according to Strauss et al. (Strauss et al. 1951).

Statistics. The results are expressed as arithmetic means + SD. For statistical analysis we used the ANOVA (Microcal ORIGIN 3.5 software). The null hypothesis was rejected when P<0.05.

RESULTS

The results are summarized in figures 2 - 9.

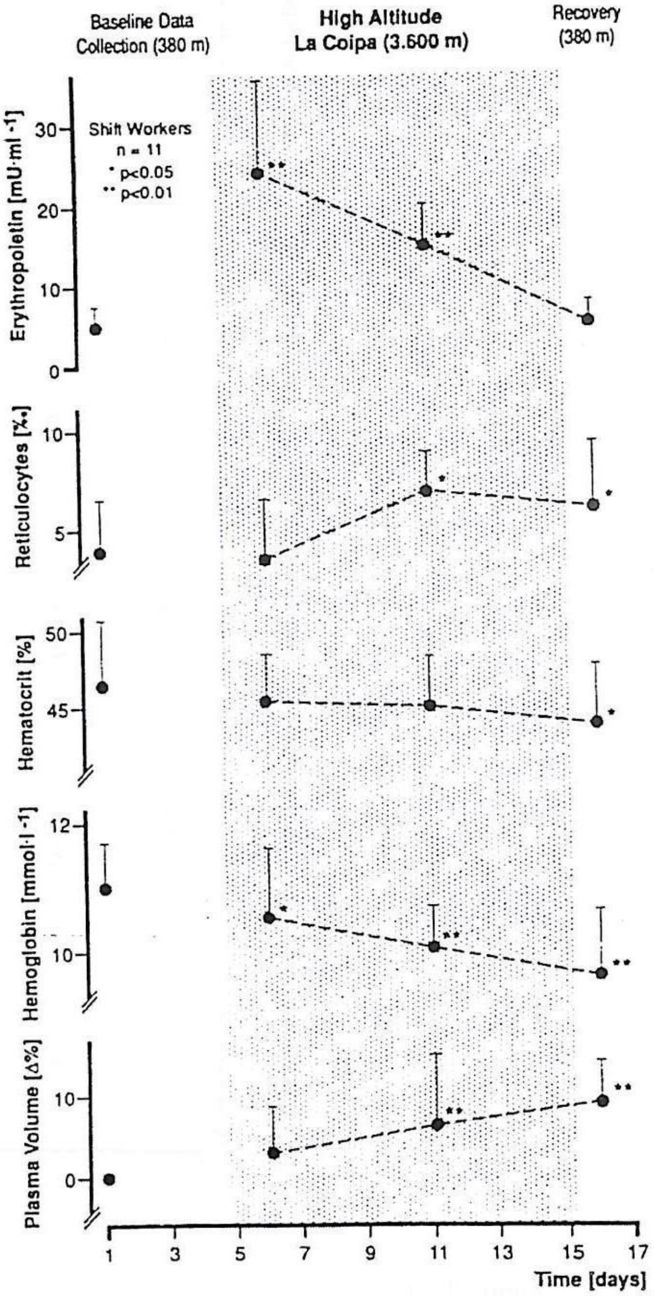

Figure 2. Erythropoietin, reticulocytes, hematocrit, hemoglobin and A% plasma volume changes in Chilean high altitude shift workers before, during, and after 10 working-days at 3,600 m. The time of

exposure to high altitude is shaded (Pc0.05; P<0.01). (After Guno,a et al.1996).

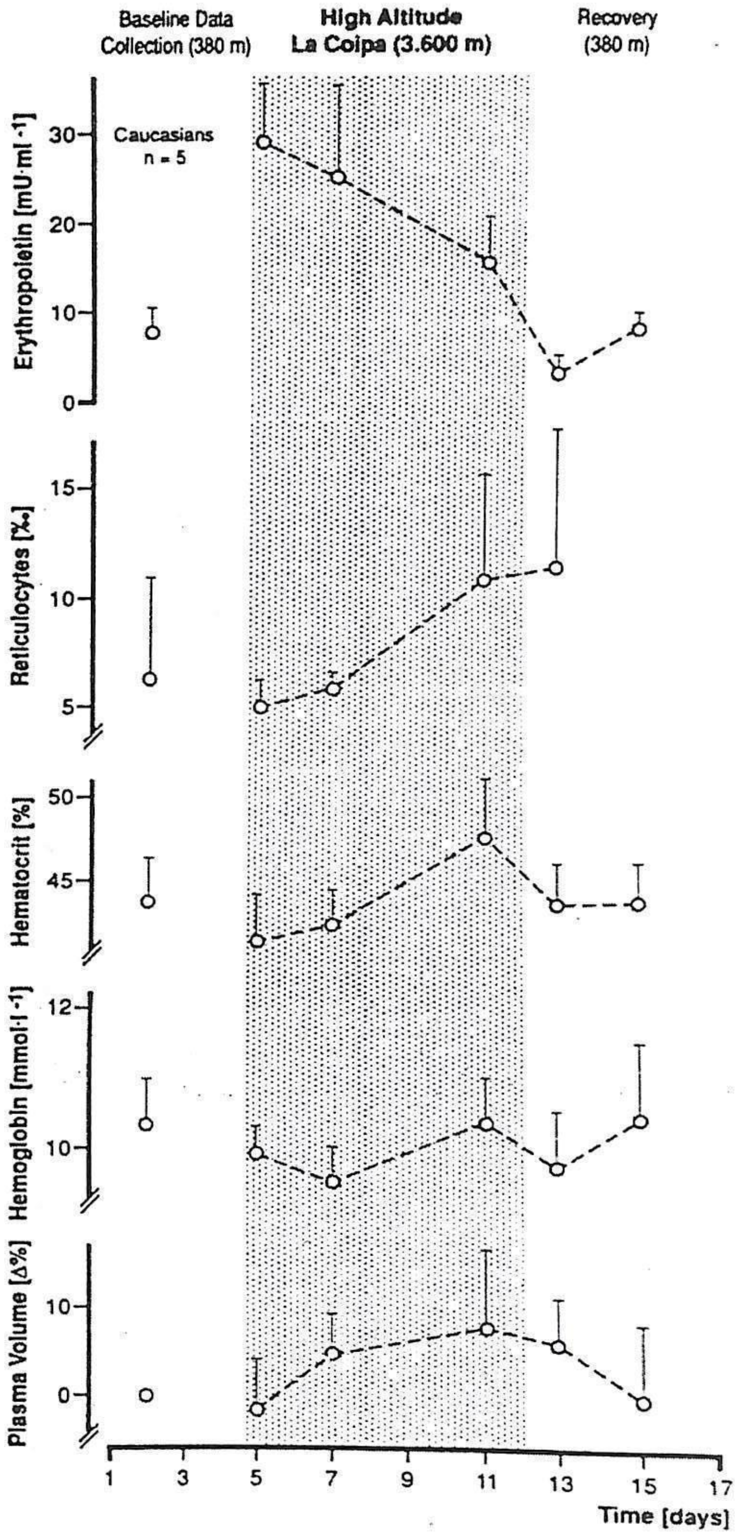

Figure 3. Erythropoietin, reticulocytes, hematocrit, hemoglobin and Δ% plasma volume changes in Caucasian low-landers before, during, and after exposure to 3,600 m. The time of exposure to high altitude is shaded. (After Gunoa et al.1996).

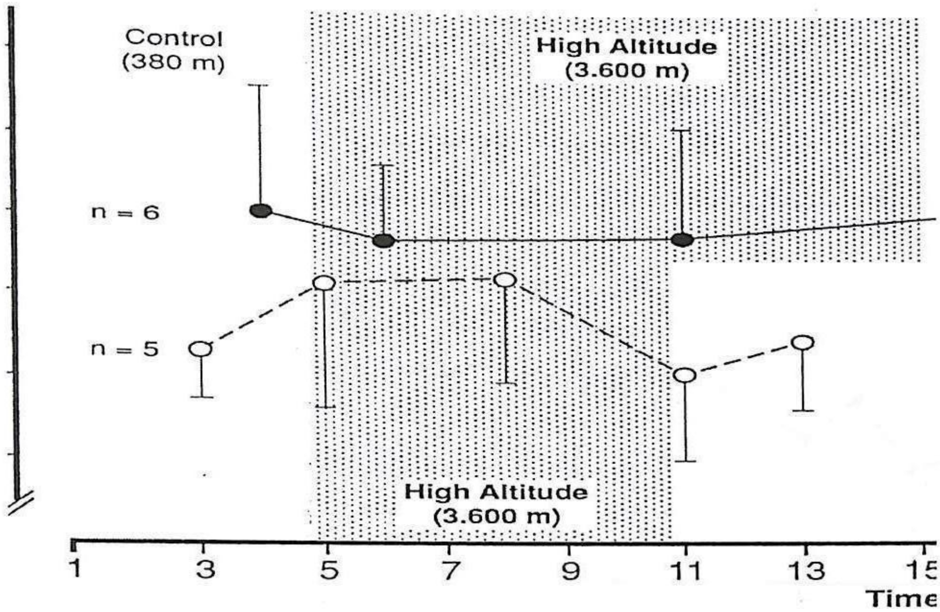

Figure 4. Central venous pressures (CVP) before, during, and after transition from sea-level (380 m) to high altitude (3,600 m) in Chilean high altitude shift workers (•) and Caucasian low-landers (o). (After Gunga et al. 1996)

DISCUSSION

Populations living permanently at high altitude (Quechua Indians, Sherpas) and newcomers (mainly Caucasian mountaineers) have been studied frequently with respect to their adaptation to different altitudes. These studies usually deal with the typical characteristics of altitude adaptations such as erythropoiesis, and cardiorespiratory control at rest and during exercise. Knowledge on high altitude adaptations in these two groups have been reported, but no systematic studies are available in the literature on the effect of professional long-term, high altitude shift working in humans as described in the present paper.

Therefore, the present study focusses on the characteristics of high altitude adaptation in humans induced by weekly altitude shifts (intermittent hypoxic stress) over of period of years rather than days or weeks (expeditions) or generations (Quechua, Sherpas) regarding the erythropoietic response as seen in EPO production and release.

The most prominent findings in this field study are 1) the low EPO concentrations at the baseline data collection in Chilean shift workers, 2) the pronounced initial EPO increase after transition from 380 m to 3,600 m, 3) the decline of EPO in both groups during the prolonged high altitude exposure, 4) the higher CVP found in high altitude shift workers compared with the controls, 5) the increase in tissue thickness at the front during high altitude exposure, and 6) the fall in COP and ALB concentrations in shift workers at altitude.

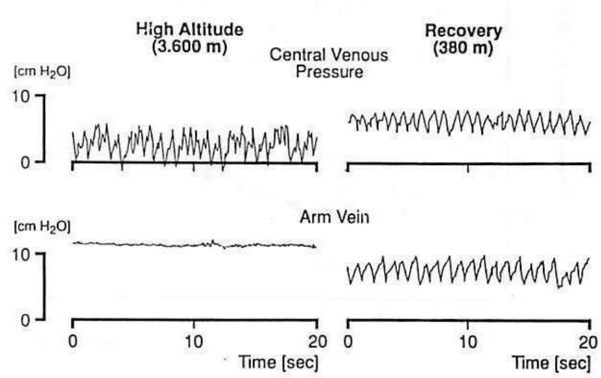

Figure 5. Typical example of central venous and peripheral arm vein pressure recordings in one subject (Chilean shift worker). High altitude left

side, 24 hours after descent right side. (After Gunga et al.1996).

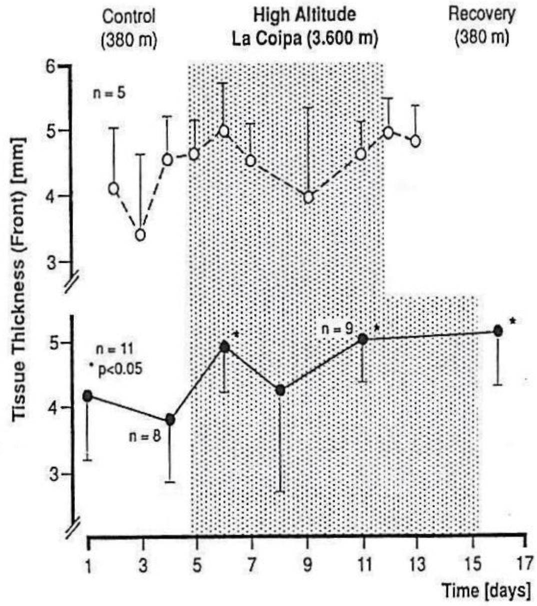

Figure 6. Time course of tissue thickness of the front (head) before, during, and after transition from sea-level (380 m) to high altitude (3,600 m) in Chilean high altitude shift workers (•) and Caucasian low-landers (o). The time of exposure to high altitude is shaded (P<0.05).

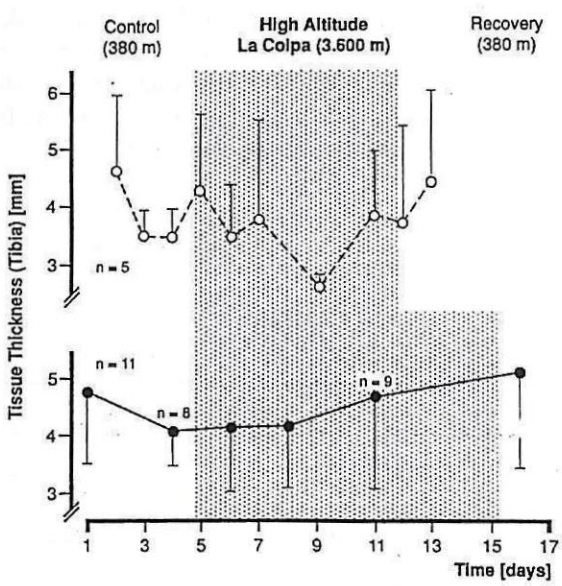

Figure 7. Time course of the tissue thickness at the tibia before, during, and after transition from sea-level (380 m) to high altitude (3,600 m) in Chilean high altitude shift workers (•) and Caucasian low-landers (o). The time of exposure to high altitude is shaded.

It is currently believed that the increase in plasma EPO concentrations is proportional to the severity of the hypoxic stress and that EPO production is regulated by the relative amount of oxygen available to the tissues involved in its production, primarily the renal cortex (Jelkmann 1992). Studies concerning the relationship between hypoxia and EPO production and release are frequent, but they were mainly performed in rodents, often used extreme pathophysiological models and therefore no data are available on EPO levels in shift workers (Jelkmann 1992). So first, a comparison between the basal EPO levels found in shift workers before transition to altitude with a larger group of male Caucasian subjects (N=49) showed that the EPO levels at the baseline data collection were significantly lower in Chilean shift workers than in Caucasian low-landers (Gunga et al. 1996). Furthermore, it appears that between 2,300-4,000m, parallel to decreasing PO2, only a slow progressive serum EPO in crease occurs. This is in accordance with the findings from hypobaric chamber studies in humans (Eckardt et al. 1989), although a field study at 4559 m showed generally lower EPO levels than observed in the present study (Mairbaurl et al.1986). This might be due to the fact that miners and Caucasian controls worked during daytime between 3,600 and 4,000 m and slept during the night at 3,000 m, so that they had a daily intermittent hypoxic stress. Significantly higher EPO levels were found in mountaineers at altitudes >5,000 m (Milledge and Cotes 1985; Richalet 1994) than in the present study.

In both the shift workers and the Caucasians, a gradual EPO concentration decrease was observed during their stay at 3,600 m, although the hypoxic stress is prevailed. This decline in EPO concentrations during the stay at high altitude is an observation, which is consistent with findings reported from moderate altitude (<2,300 m) (Gunga et al. 1994) and higher altitudes (Abbrecht and Littell 1972; Milledge and Cotes 1985; Richalet et al. 1994). The EPO down-regulation is surprisingly similar in shift workers and Caucasians. It was previously suggested (Winslow and Monge 1987) that at this altitude, the rate of EPO turnover could be increased after initial stimulation, precluding its accumutation in the blood. Nutritional factors, such as a low protein and/or carbohydrate intake (Anagnostou et al. 1977; Bethard et al. 1958; Catchatourian et al. 1980; Rosenberg et al. 1989), as a reason for the decline in serum EPO concentrations during the stay at high altitude, which first was theoretically predicted (Dunn et al. 1980), can be excluded during this study; the mine management took care that a sufficient food supply was guaranteed so that each subject received approximately 50-60 kcal - cal[1] 24 hrs. Therefore, our data support the findings of a single earlier study, which came to the conclusion that the fall of the EPO concentration during continuous hypoxia is not primarily related to reduced food intake (Jelkmann et al.1983).

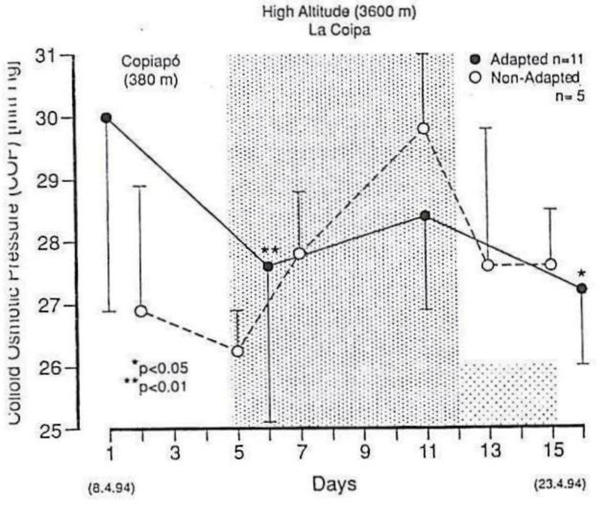

Figure 8. Time course of the colloid osmotic pressure before, during, and after transition from sea-level (380 m) to high altitude (3,600 m) in Chilean high altitude shift workers (•) and Caucasian low-landers (o). The time of exposure to high altitude is shaded (P<0.05; P<0.01).

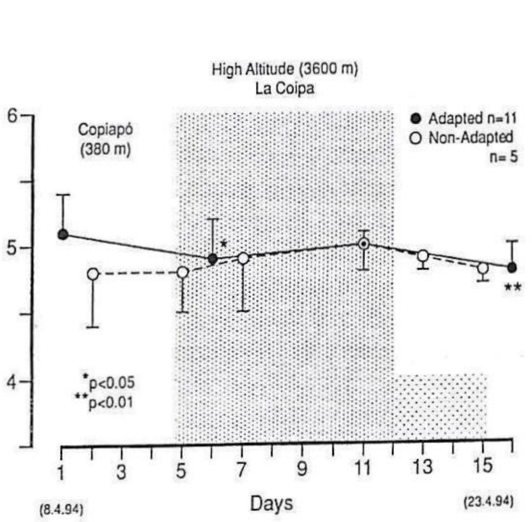

Figure 9. Time course of albumin concentrations before, during, and after transition from sea-level (380 m) to high altitude (3,600 m) in Chilean high altitude shift workers (•) and Caucasian low-landers (o). The time of exposure to high altitude is shaded (P<0.05; P<0.01).

Baseline hematocrit in Chilean shift workers was slightly higher than in the Caucasian control group, but rather low compared to hematocrit values known from rural and urban populations living permanently at altitudes >3,000 m in Bolivia, Peru and Chile (hematocrit >50%) (Monge et al. 1990; Winslow et al. 1989; Winslow and Monge 1987). In contrast, the baseline hemoglobin concentrations of shift workers were comparable to those found in the literature for high altitude populations (Monge et al.1990; Winslow and Monge 1987).

Previous experimental data in dogs have shown that changes in CVP modulate EPO production and release (Ehmke et al. 1995; Just et al. 1993), and similar considerations were made for man (Gunga et al. 1994). According to this hypothesis, changes in CVP should be inversely related to EPO concentrations in blood, i.e. low CVP should lead to an increase in EPO concentrations and vice versa. We tested this hypothesis in the shift workers and the Caucasian control group. Little if any data on the CVP at altitude has been reported in the literature. During Operation Everest II, a simulated ascent to Mount Everest in a hypobaric chamber over 40 days, the surprising observation was made that the mean right atrial pressures tended to be low despite pulmonary hypertension. Compared with sea-level values it was found that high altitude right atrial pressures were decreased for 10 of the 15 resting and for 20 of 23 exercise measurements (Reeves et al. 1987).

The venous recordings in the present study support the idea that the shift workers had a high intrathoracic filling volume, because the CVP values were generally higher than in the low-landers (Figure 4). Furthermore, the wave forms seen in the arm vein after descent indicate that the high filling volume had overcome the collapse of the veins at the point where they enter the thorax (Figure 5). Therefore, the pressure gradient between the intra- and the extrathoracic part of the low pressure system was small, so that both parts of the low pressure system form a unit. This can either occur via high intravascular volume or venous constriction, which moves the blood volume from the extra- towards the intrathoracic vessels or both.

In general, CVP in the shift workers tended to decrease at high altitude. That this was not seen in the Caucasian controls in this study might be due to the fact that the subjects tended to be dehydrated or that they had vasodilation due to the acclimatisation to the Atacama desert climate (Adolph 1969).

In this study at high altitude fluid extravasations into the superficial tissues of the upper part of the body occured whereas at the lower part of the body (tibia) no significant changes could be detected by the ultrasound method (figure 6 and 7). Simultaneously in shift workers a significant fall of COP and ALB could be observed and it might well be that this fall in intravascular COP is obviously partly due to a protein leakage supporting edema formation in the superficial tissues of the upper part of the body. Those peripheral edemas at high altitude are described frequently (Hackett et al. 1976; Hayashi et al. 1988; Lobenhofer et al. 1982) and data concerning the water turnover, body composition and protein concentrations at high altitude are also available in the literature (Bartsch et al. 1991; Claybaugh et al.1992; Hannon et al.1969; Kryzwicki et al. 1971; Rennie et al. 1972; Surks et al. 1966). In the present study, the ultrasound sensors were attached at points were the underlying tissues consisted predominantely of skin and connective tissues. These tissues are known to be water stores of the body among others (Aukland and Reed 1993). In case the hydration level of the body changes in these tissues the first signs are visible there, provided thermoneutral conditions prevailed so that noteworthy changes of the skin perfusion can be excluded. We could demonstrate this in patients during dialysis treatment and in women during pregnancy and after delivery. In those models within short periods water loading of the tissues and unloading can be followed. With the help of the method these changes could be reliably seen (Kirsch et al. 1993; Gunga et al. 1994; Gunga et al. 1995). Why the edema preventing mechanisms as proposed by Guyton and co-workers (Guyton et al. 1975) got out of control at high altitude remains an open question. The fact remains that the fluid accumulation in the peripheral tissues went hand in hand with a protein leakage which concomitantly led to a decrease in COP. It is tempting to speculate that not only the superficial tissue in the upper part of the body are involved in this fluid accumulation but probably also lung and other tissues of the body. Hackett and Rennie (Hackett and Rennie 1979) described recentiy among other phenomenas the occurrence of peripheral edema in mountaineers. They stated that peripheral edemas are a common problem at altitude and sometimes very dramatic. Out of 200 trekkers they found 23 % having at least in one area of the body peripheral edema. The edemas in their group occurred as well around the eyes and face, the hands, or the ankies and feet. Furthermore, they found that 14 out of 19 who had facial edema had as well signs of acute mountain sickness. Some of the trekkers had eyelid edema which was so extensive that vision was impaired. They came to the conclusion that everyone with peripheral edema must be checked for pulmonary (HAPE) and cerebral edema (HACE) as well. Lobenhofer et al. (1982) who analysed 166 cases of high altitude pulmonary edema found in 10 cases (7 %) local edema. Hayashi et al. (1988) who studied the changes in water balance and in arterial oxygen saturation in 28 trekkers during a mountaineering expedition to Mt.Tharkot (6 100 m) in india found an increased incidence of peripheral edema despite a reduction in total water consumption and the use of Diamox during the ascending phase. In their study peripheral edema occurred from 2 500 m on and the incidence increased with higher altitude. In their study the two subjects who suffered most severly from high altitude exposure showed retinal hemorrhages, coughing and peripheral edema. Carson et al. (1969) who investigated a group at Pike's Pike determined the number and time course of symptoms of the acute mountain sickness (AMS) appearing during a stay at high altitude. They found that the subjects had the most severe symptoms on the 1st and 2nd day at high altitude. It remains to be seen whether the application of this new, non-invasive superficial tissue "edema-detector" can be used as an indicator in case such a fatal development starts.

In conclusion, the hypothesis has to be refuted that the initial EPO response to a hypoxic stimulus equivalent to 3,600 m is altered in Chilean shift workers during a five year period of intermittent hypoxic stress. The EPO concentrations in long-term shift workers are lowered at BDC compared to a large Caucasian control group. The low EPO concentrations found at BDC might be related to higher hemoglobin concentrations or generally higher CVP found in this group compared to the Caucasian controls. Changes in CVP, fluid shifts out of the intravascular compartment and their accumulation in the interstitial space as well as the decrease in COP and ALB concentrations during the altitude exposure deserve further investigations to unterstand the role of the low pressure system in human adaptation to moderate and high altitude.

We are indebted to the mining management and the kitchen personnel of La Copia. Furthermore, we would like to thank Mrs. Brigitte Bunsch, Mrs. Christine Felix, Mrs. Brigitte Heyduck, Mrs. Ozlem Gurvit, Mrs. Helga Semmler and Mr. Hans Jurgen Wicke for their technical assistance.

This research was supported by grant No. 50 WB 93773 from the Bundesministerium fur Bildung, Wissenschaft, Forschung und Technologie (BMBF, Bonn), Deutsche Agentur fur Raumfahrtangelegenheiten (DARA, Deutsche Forschungsgemeinschaft (DFG) grant No. B6 Hi

581/1-1, and by Fondo Nacional de Desarollo Cientifico y Tecnológico (FONDECYT, Chile) grant No. 1950454.

Parts of this article are based on the papers "Fluid distribution and tissue thickness changes in 29 men during 1 week at moderate altitude (2,315 m)" by Gunga et al. (European Journal of Applied Physiology, January 1995) and "Shift working at high altitude and its influence on erythropoietin and the low pressure system" by Gunga et al. (Journal of Applied Physiology, August 1996).

REFERENCES

1. Abbrecht, P. H., J. K. Littell. Plasma erythropoietin in men and mice during acclimatization to different altitudes. J. Appl. Physiol. 32: 54-58, 1972.
2. Adolph, E. F. Physiology of man in the desert. Reprint New York - London: Hafner Publishing Company, 1969.
3. Anagnostou, A., S. Schade, M. Ashkinaz, J. Barone, W. Fried. Effect of protein deprivation on erythropoiesis. Blood 50: 1093-1097, 1977.
4. Aukland K., R. K. Reed. Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. Physiol. Rev. 73: 1-78, 1993.
5. Bartsch P., N. Pfluger, M. Audétat, S. Shaw, P. Weidmann, P. Vock, W. Vetter, D. Rennie, O. Oeiz. Effects of slow ascent to 5,559 m on fluid homeostasis. Aviat. SpaceEnviron. Med. 62:105-110,1991.
6. Bartsch P., S. Shaw, P. Weidmann, M. Franciolli, M. Maggiorini, O. Oelz. Aldosterone, antidiuretic hormone, and atrial natriuretic peptide in acute mountain sickness. In: Sutton J. R., G. Coates, and C. S. Houston (eds). Hypoxia and mountain medicine, Hypoxia Symposium 1991. Queen City Printers Inc., Burlington, Vermont, pp 73-81, 1992.
7. Bethard, W. F., R. W. Wissler, J. S. Thompson, M. A. Schroeder, M. J. Robson. The effect of acute protein deprivation upon erythropoiesis in rats. Blood 13: 216-225.1958.
8. Carson R. P., W. O. Evans, J. L. Shields, J. P. Hannon. Symptomatology, pathophysiology, and treatment of acute mountain sickness. Fed. Proc. 28:1085-1091,1969.
9. Catchatourian, R., G. Eckerling, W. Fried. Effect of short-term protein deprivation on hematopoietic functions of healthy volunteers. Blood 55: 625628,1980.
10. Claybaugh J.R., D. P. Brooks, A. Cymerman.: Hormonal control of fluid and electrolyte balance at high altitude in normal subjects. In: Sutton J. R., G. Coates, and C. S. Houston (eds). Hypoxia and mountain medicine, Hypoxia Symposium 1991. Queen City Printers, Burlington, Vermont, pp 61-72,1992.
11. Dunn, C. D. R., L. N. Smith, J. I. Leonard, R. B. Andrews, R. D. Lange. Animal and computer investigations into murine erythroid response to chronic hypoxia. Exp. Hematol. 8 (Suppl 8): 259-279,1980.
12. Eckardt, K.-U., U. Boutellier, A. Kurtz, M. Schopen, E. A. Koller, C. Bauer. Rate of erythropoietin formation in humans in response to acute hypobaric hypoxia. J. Appl. Physiol. 66: 1785-1788,1989.
13. Ehmke, H., A. Just, K.-U. Eckardt, P. B. Persson, C. Bauer, H. R. Kirchheim. Modulation of erythropoietin formation by changes in blood volume in conscious dogs. J. Physiol. (London) 488: 181-191,1995.
14. Frisancho, A. R. Origins of differences in haemoglobin concentration between Himalayan and Andean populations. Respir. Physiol. 72: 13-18, 1988.
15. Gauer, O. H., H. O. Sieker. The continuous recording of central venous pressure changes from an arm vein. Circ. Res. 4: 74-78,1956.
16. Gunga, H.-C., K. Kirsch, L. Rocker, W. Schobersberger. Time course of erythropoietin, triiodothyronine, thyroxine, and thyroid-stimulating hormone at 2,315 m. J. Appl. Physiol. 73: 1068-1072,1994.
17. Gunga, H.-C., K. Kirsch, L. Rocker. Central venous pressure and erythropoietin after spaceflight (Letter). Aviat. Space Environ. Med. 65: 274, 1994.
18. Gunga H.C., F. J. Baartz, I. Herrenleben, K. Kirsch. Fluid recruitment from shell tissues of the body during haemodialysis. Nephrol. Dial. Transplant. in press,1994.
19. Gunga, H.-C., K. Kirsch, F. Baartz, H.-J. Steiner, P. Wittels, L. Rocker. Fluid distribution and tissue thickness changes in 29 men during one week at moderate altitude (2,315 m). Eur. J. Appl. Physiol. 70:1-5,1995.
20. Gunga, H.-Chr., L. Rocker, C. Behn, W. Hildebrandt, E. Koralewski, I. Rich, W. Schobersberger, K. Kirsch. Shift working in the Chilean Andes (>3,600 m) and its infiuence on

erythropoietin and the low pressure system. J. Appl. Physiol., in Press 1996.

21. Guyton A. C., A. Taylor, H. Granger. Circulatory physiology. Dynamics and control of the body fluids. Saunders, Philadelphia,1975.

22. Hackett P., D. Rennie. The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 2: 1149- 1155.1976.

23. Hackett P.. D. Rennie. Acute mountain sickness. Lancet 1 :491, 1977.

24. Hackett P., D. Rennie. Rales, peripheral edema, retinal hemorrhage and acute mountain sickness. Am. J. Med. 67:214-218,1979.

25. Hannon J. P., K. S. K. Chinn, J. L. Shields. Effects of acute high-altitude exposure on body fluids. Fed. Proc. 28:1178-1184,1969.

26. Hayashi R., A. Seko, G. Mitarai. Peripheral edema and retinal hemorrhage in Himalayan climbers. In: Ueda G., S. Kusama, and N. F. Voelkel (eds). High altitude medical science. Shinsu University, Matsumoto, pp 318-322, 1988.

27. Jalil, J., P. Casanegra, S. Braun, G. Chamorro, F. Saldfas, T. Berofza, A. Foradori. Working at high altitude in Andean miners from Chile: Human adaptation to long term intermittent hypobaric hypoxia. In: Sutton J. R., C. S. Houston, and G. Coates (eds). Hypoxia and the brain, Symposium 1995. Queen City Printers Inc., Burlington, Vermont, pp 284-291,1995.

28. Jimenez D. High altitude intermittent chronic exposure: Andean miners. In: Sutton J. R., C. S. Houston, and G. Coates (eds). Hypoxia and the brain, Symposium 1995. Queen City Printers Inc., Burlington, Vermont, pp 284-291, 1995.

29. Jelkmann, W., A. Kurtz, C. Bauer. Effects of fasting on the hypoxia-induced erythropoietin production in rats. PflugersArch. 396: 174-175,1983.

30. Jelkmann, W. Erythropoietin: Structure, control of production, and function. Physiol. Rev. 72: 449-489,1992.

31. Just, A., H. Ehmke, P. B. Persson, U. Eckardt, A. Kurtz, H. R. Kirchheim. Infiuences of changes in central venous pressure on the regulation of plasma erythropoietin concentration in conscious dogs. In: Abstracts of the XXXII Congress of the Intemational Union of Physiological Sciences. Am. J. Physiol. 32: F925.1993.

32. Kirsch K., J. Merke, H. Hinghofer-Szalkay, M. Barnkow, H. J. Wicke. A new miniature plethysmograph to measure volume changes in small circumscribed tissue areas. PflugersArch. 383:189-194,1980a.

33. Kirsch K., J. Merke, H. Hinghofer-Szalkay. Fluid distribution within superficial shell tissues along body axis during changes of body posture in man. Pflugers Arch. 383:195-201,1980b.

34. Kirsch, K., Rocker L., Gauer O. H., Krause R., Leach, H. J. Wicke, R. Landry. Venous pressure in man during weightlessness. Science 225: 218219. 1984.

35. Kirsch K., F. J. Baartz, H. C. Gunga, L. Rocker. Fluid shifts into and out of superficial tissues under microgravity and terrestrial conditions. Clin. Investig. 71:687-689.1993.

36. Kryzwicki H. J., C. F. Consolazio, H. L. Johnson, W. C. Nielsen, R. A. Barnhart. Water metabolism in humans during acute altitude exposure (4300 m). J. Appl. Physiol. 30:806-809,1971.

37. Laurent T. C. Structure, function and turnover of the extracellular matrix. Adv. Microcirc. 13: 15-34,1987.

38. Lobenhofer H. P., R. A. Zink, W. Brendel. High altitude pulmonary edema: Analysis of 166 cases. In: Brendel W, Zink RA (eds) High Altitude Physiology and Medicine. Springer, Berlin Heidelberg New York, pp 219-231,1982.

39. Mairbaurl, H., W. Schoibersberger, E. Humpeler, W. Hasibeder, W. Fischer, E. Raas. Beneficial effects of exercising at moderate altitude on red cell oxygen transport and on exercise performance. Pflugers Arch 406: 594-599,1986.

40. Milledge, J. S., P. M. Cotes. Serum erythropoietin in humans at high altitude and its relation to plasma renin. J. Appl. Physiol. 59: 360-364,1985.

41. Monge, C., D. Bonavia, F. León-Velarde, A. Arregui. High altitude populations in Nepal and the Andes. In: Hypoxia -The adaptations. J. R. Sutton, J. R., G. Coates, and J. E. Remmers (eds.). Toronto: Decker, 53-58,1990.

42. Reeves, J. T., B. M. Groves, J. T. Sutton, P. D. Wagner, A. Cymerman, M. K. Malconian, P. B. Rock, P. M. Young, C. S. Houston. Everest II: Preservation of cardiac function at extreme altitude. J. Appl. Physiol. 63: 531 -539, 1987.

43. Rennie D., R. Frayser, G. Gray, C. Houston. Urine and plasma proteins in men at 5.400 m. J. Appl. Physiol. 32:369-373,1972.

44. Richalet, J.-P., J.-C. Souberbielle, A.-M. Antezana, M. DTchaux, J.-L. Le Trong, A. Bienvenu, F. Daniel, C. Blanchot, J. Zittoun. Control of erythropoiesis in humans during prolonged exposure to the altitude of =,542 m. Am. J. Physiol. 266: R756-R764,1994.

45. Rosenberg, M. E., R. B. Howe, E. D. Zanjani, T. H. Hostetter. The response of erythropoietin to dietary protein in human renal disease. J. Lab. Clin. Med. 113: 735-742.1989.

46. Sachs L.. Angewandte Statistik, Planung und Auswertung, Methoden und Modell. Springer, Berlin, Heidelberg, New York, 1974.

47. Strauss, M. B., R. K. Davis, J. D. Rosenbaum, E. C. Rossmeisl. Water diuresis produced during recumbency by the intravenous infusion of isotonic saline solution. J. Clin. Invest. 30: 862-868,1951.

48. Surks M. I., K. S. K. Chinn, L. R. O. Matoush. Alterations in body composition in man after acute exposure to high altitude. J. Appl. Physiol. 21:1741-1746, 1966

49. Sylvester H., C. Palacios. Transpressional structures in the Andes between the Atacama Fault Zone and the West Fissure System at 27! S, III. Region, Chile. Zbl. Geol. Palaont. Teill, =:1645-1658,1992.

50. Ward, M. P., J. S. Milledge, J. West. High altitude medicine and physiology. London: Chapman & Hall, 1995.

51. Winslow, R. M., K. W. Chapman, C. C. Gibson, M. Samaja, C. C. Monge, E. Goldwasser, M. Sherpa, F. D. Blume, R. Santolaya. Different hematologic responses to hypoxia in Sherpas and Quechua Indians. J. Appl. Physiol. 66: 1561-1569, 1989.

52. Winslow, R. M., C. Monge. Hypoxia, polycythemia and chronic mountain sickness. Baltimore: John Hopkins University Press, 1987.