

The effect of maternal exercise and altitude training on performance in hypoxic environment: a brief review

He Long Quan^{ab*} & Chang Keun Kim^{ab}

^a*Exercise and Metabolism Research Centre, Zhejiang Normal University, Jinhua, China*

^b*College of Physical Education and Health Sciences, Zhejiang Normal University, Jinhua, China*

Abstract

Environmental and maternal exercise experienced even during the very earliest stages of life has the potential to cause developmental changes. The growing evidence demonstrated that diverse environmental stressors affect offspring in various aspects in early stage of life and can be transmitted directly or indirectly by both parental lines. The development of normobaric hypoxic environment facilities began in recent years after athletes born and trained at high altitude continued to update their records in sports competition, especially marathons and other endurance sports. Although a large number of studies have proved the effect of hypoxic training in the field of sports science and competition, the effectiveness of this training model on exercise performance/capacity and physiological variables is still controversial. Therefore, this study makes a brief review of the papers related to this scope and attempted to understand the potential mechanism of maternal exercise in hypoxic environment on exercise performance and reduction of metabolic risk factors.

Key words: hypoxia, hypoxic environment, maternal exercise, exercise performance, metabolic syndromes

Introduction

The development of normobaric hypoxic environment facilities began in recent years after athletes born and trained at high altitude continued to update their records in sports competition, especially marathons and other endurance sports. The influence of hypoxic environment on competitive ability has aroused great interest. In preparation for the Mexico Olympics in 1968 that was to be held at an altitude

of 2,400 m above sea level, countries with advanced sports performance began to explore methods to adapt to and train in various hypoxic environments. Most of the studies on the human body exposed in high altitude nature environments are carried out by mountaineering experts or athletes to adapt to high altitude training (Loshbaugh, Loeppky, & Greene, 2006; Schena, Guerrini, Tregnaghi, & Kayser, 1992). However, even after 50 years of extensive research on energy metabolism after temporary high-altitude training in athletes born, raised, and trained at sea level, the reasons behind the failure to parallel the athletic performance of athletes born, raised, and trained at a high altitude

remain elusive. In addition, due to exposure to high altitude will cause acute mountain sickness(AMS), cold, decreased physical function and other stress reactions, the application of high altitude nature environment has some limitations, it is difficult to be widely used in ordinary people(Benso et al., 2007; Florian, Jankowski, & Gutkowska, 2010).

People who live at sea level are also known to lose weight when they are exposed to high altitudes, that is, a hypoxic environment(Armellini et al., 1997; Benso et al., 2007; Fusch et al., 1996; Major & Doucet, 2004). Further, cellular hypoxia induced by exposure to hypoxic environment occasionally occurs in people who emigrated to a high-altitude region. It not only shows the major pathological and physiological characteristics of diseases such as heart failure and chronic obstructive pulmonary disease but also may cause an imbalance of protein synthesis/degradation in skeletal muscles, energy metabolic impairment, and muscle cell apoptosis, ultimately leading to skeletal muscle atrophy and weakening of muscle capacity(Murray, 2009).

However, exercise training under hypoxia conditions is known to have several benefits, including increased in blood levels of red blood cell(RBC), hemoglobin(Hb), and hematocrit (Hct)(Chapman, Stray-Gundersen, & Levine, 1998), increased in the density of vascular endothelial growth factor (VEGF) (Harris, 2002; Semenza, 1998), myoglobin(Hahn & Gore, 2001), mitochondria and capillaries density in muscle(Desplanches et al., 2014; Desplanches et al., 1993; Hoppeler, Klossner, & Vogt, 2008; Lundby, Calbet, & Robach, 2009), and the transport and utilization of oxygen in skeletal muscle, improvement angiogenesis and muscle capillarization(Vogt & Hoppeler, 2010); as well as in the biosynthesis and phosphorylation of mitochondria in skeletal muscle(Bo, Zhang, & Ji, 2010).

From this perspective, sports science researchers have begun to explore various adaptation and training methods in hypoxic environments to enhance performance at higher altitudes in preparation of the

Mexico Olympics in 1968, which was to be held at 2,400 m above sea level. These strategies include intermittent hypoxic training (IHT), living high - training low (LHTL), living low - training high (LLTH), living high - training high (LHTH), and living high - exercise high - training low (LHEHTL). However, which of these training methods is the most effective method to optimize aerobic exercise capacity for athletes remains controversial(Desplanches et al., 1993; Levine, 2002; Levine & Stray-Gundersen, 1997, 2001).

The failure to reach a consistent conclusion among studies is mainly attributable to the differences in participant selection, altitude for training, intensity and duration of training at high altitude, and selected measurement variables. However, most of all, this is a result of assessing the outcomes of high-altitude training after living at a high altitude only temporarily or simply comparing with athletes who were born and trained at a high altitude.

Maternal exercise and Hypoxic environment

Both genetic and environmental factors influence human growth and development. Environmental factors are involved in development in early life, and they have growth and developmental potential beyond the limitations of genetic traits(Aiken & Ozanne, 2014; Gilbert, 2001; Patti, 2013; Susser et al., 2012). Studies have reported that the genetic characteristics of conspecifics and effects of the range of viable environment, that is, exercise, nutrition, or environmental regulation during the conception process are intimately associated with growth and health of the subsequent generation(Moore et al., 2004).

Previous studies from the perspective of nutrition have pointed out that excessive calorie intake before pregnancy may lead to obesity and muscle weakness in offspring(Bayol, Macharia, Farrington, Simbi, & Stickland, 2009; Bayol, Simbi, Bertrand, & Stickland, 2008; Ng et al., 2010), while limiting maternal protein

intake may lead to low birth weight and metabolic dysfunction in adulthood (Ng et al., 2010; Peixoto-Silva, Frantz, Mandarim-de-Lacerda, & Pinheiro-Mulder, 2011).

Although several studies have been conducted, the impact of maternal exercise on offspring after birth is yet to be elucidated, except for some studies finding that exercise during pregnancy has significant impacts on the mother and fetus. Some recent studies confirmed that prenatal and postnatal endurance exercise has a positive impact on child's body composition and glucose and insulin metabolism (Carter et al., 2012; Carter, Qi, De Cabo, & Pearson, 2013; Pinto & Shetty, 1995). On the other hand, however, one study reported that maternal exercise training lowers neonatal body weight by reducing percent body fat (Clapp & Capeless, 1990; Kalisiak & Spitznagle, 2009).

In a sense, hypoxic environment is a physiological challenge and an environmental stress condition that induces organisms' adaptation, and natives of highlands have genes adjusted to the hypoxic environment (Michiels, 2004). In highlands, organisms undergo a homeostatic reaction to the shortage of oxygen, which helps them adjust to the high-altitude environment, and such adaptation may influence subsequent generations as a genetic factor (Ge et al., 1994).

Moreover, the theory of evolution explains pregnancy as an important stage that establishes the genetic traits of the fetus, and abnormal fetal growth in the uterus may increase the risk of cardiovascular diseases (Moret, Covarrubias, & Coudert, 1971). Based on these phenomena, hypoxic environment has been a major topic of research in the studies of ecology and evolution (MacInnis & Rupert, 2011; Mousseau & Fox, 1998; Uller, 2008), and the impact of maternal or paternal exercise training on subsequent generations has attracted much research interest in the field of sports medicine. Interestingly, physical performance declines with increasing altitude, but natives who have lived in highlands over several generations have been confirmed to have superior physical performance to that of people

who emigrated to highlands (Sun et al., 1990; Weitz, Liu, He, Chin, & Garruto, 2013).

Such physical superiority of natives of highlands may be an ethnic feature, but it may also be a result of secondary adaptation to hypoxic environment. It is a fact that residents of highlands often have an elevated red blood cell count, such as polycythemia, to deliver oxygen and high myoglobin, mitochondria, and capillary density in muscles, thereby having an enhanced ability to transport oxygen to tissues and utilize oxygen in tissues.

Considering the reality in which athletes from some African countries who were born, raised, and trained in highlands at 2,000-3,000 m above sea level lead and set world records in middle and long distance running, concurrently examining the effects of multi-generational growth and exercise training in hypoxic environment would be highly significant. In particular, considering that middle-and long-distance athletes who grow up and trained at sea level cannot compare with their peers born in a hypoxic environment in terms of sports performance, even for implemented short term exercise training at high altitude (4-16 weeks). A long-term study design over several generations is essential to assess the characteristics of athletes born accurately and assess the effects of training at high-altitude for sea level athletes.

In a recent study on 1,250 natives of highlands (Yang et al., 2016), reported that these natives have a modified HMOX2 gene. This gene suppresses the excessive elevation of red blood cells, that is, polycythemia, which may be induced by prolonged habitation in highlands, thereby maintaining red blood cell and hemoglobin levels in normal ranges. This gene enables natives of highlands to maintain an appropriate blood red blood cell and hemoglobin levels while living and during exercise training at a high altitude, rendering their training more effective compared to that of people who live at sea level. However, it is yet unclear whether this is a result of the low oxygen concentration itself or is influenced by activities in a hypoxic environment.

Maternal exercise and Mitochondria

Mitochondria, well known as the cell's "energy plant" and "energy conversion center," is one of the most critical organelles in cells (Lehman et al., 2000), and mitochondria in skeletal muscles have been reported to be more heavily influenced by maternal DNA (Newgard, Hwang, & Fletterick, 1989). In a cell, mitochondria take charge of the cell's physiological functions through continuous synthesis and degradation under the regulation of nuclear genes and mitochondrial genes. Mitochondrial biogenesis refers to proliferation of mitochondria during a cell cycle and mitochondrial system synthesis (Meisinger, Sickmann, & Pfanner, 2008; Taylor et al., 2003). In light of reports that elevated expression of the PGC-1 α protein in skeletal muscles and myocardial cells induces mitochondrial biogenesis, PGC-1 α is considered a classic parameter for mitochondrial biogenesis (Levett et al., 2012; Little, Safdar, Bishop, Tarnopolsky, & Gibala, 2011; Pilegaard, Saltin, & Neufer, 2003). Elevated expression of the PGC-1 α protein in skeletal muscles is accompanied by elevated expression of the NRF-1, mtTFA, and COX-IV proteins, and such elevation has been observed to increase the number of mitochondria and biogenesis capacity (Carraway et al., 2010; Z. Wu et al., 1999).

Muscle contraction activities as a result of exercise or other external stimuli may enhance the levels of mRNA and proteins for many transcription factors and particularly, may induce mitochondrial biosynthesis (Hood et al., 2003; Irrcher, Adhietty, Joseph, Ljubicic, & Hood, 2003). PGC-1 α (peroxisome proliferator-activated receptor coactivator-1 α) is the classic parameter of mitochondrial biogenesis, and PGC-1 α induces mitochondrial biogenesis by stimulating the nuclear respiratory factor-1,-2 (NRF-1,-2) and mitochondrial transcription factor A (mtTFA) (Johnson, Robinson, & Nair, 2013)). Further, COX-IV is an indicator of oxidative phosphorylation in mitochondria and aerobic exercise capacity and is

regulated by NRF (Geng et al., 2010). Muscle contraction caused by one-time exercise or exercise training is known to enhance mitochondrial biogenesis and functions via expression of proteins such as PGC-1 α and COX-IV (Demory et al., 2009; Jiandie Lin, Handschin, & Spiegelman, 2005; J. Lin et al., 2002; Miura et al., 2006; Terada & Tabata, 2004). In addition, training in hypoxic environment has been reported to increase expression of some proteins (Chitra & Boopathy, 2014; Desplanches et al., 1993; Geiser et al., 2001; Melissa, MacDougall, Tarnopolsky, Cipriano, & Green, 1997; Terrados, Jansson, Sylven, & Kaijser, 1990; Vogt et al., 2001).

Exercise is known to play an important role in enhancing the mitochondrial functions in skeletal muscles (Irrcher et al., 2003; Lanza & Nair, 2009; Short, Nair, & Stump, 2004), and improvement of mitochondrial volume and functions from exercise training has been considered an important means to boost performance of endurance athletes (Hawley & Lessard, 2008; Holloway et al., 2009).

However, not many studies have examined the effects of maternal exercise before and during pregnancy in improving mitochondrial biogenesis and functions, and particularly, studies that investigate the aerobic capacity of organisms born and raised in a hypoxic environment and the effects of multi-generational maternal endurance exercise on subsequent generations are completely lacking.

The Metabolic Characteristics of Highlanders

Commonly, the growth and height of animals or plants at high altitude regions is slower or smaller compared to sea level. The hypoxic environment also affects the energy balance and growth of animals, including humans, and the altitude that affects human function is considered at the level of 5000-5500 meters above sea level (Kayser & Verges, 2013). Recently, it has been reported that the body composition and metabolic

characteristics of highlanders have lower prevalence and metabolic risk factors of metabolic diseases than people living at sea level.

Among the Aymara tribe in Chile, where BMI is similar to those living at sea level in South America (BMI>30), but the prevalence of diabetes is said to be relatively low (Santos, Perez-Bravo, Carrasco, Calvillan, & Albala, 2001). The BMI of Tibetans living at different high altitude (1200m, 2900m and 3600 m) in Nepal and Tibet was investigated, and the effect of obesity rates was analyzed. The results showed altitude itself affects energy intake and physical activity (Sherpa et al., 2010). In other words, the hypoxic environment itself may reduce the intake of energy sources and increase energy consumption. Furthermore, Wu et al. (2007) workers (obese) involved in railway construction between Qinghai and Tibet (3000-5000 meters above sea level) returned to normal weight during 3-5 months of operation (T. Y. Wu et al., 2007). Schobersberger et al. (2003) also studied patients with metabolic diseases and found that blood pressure and metabolic risk factors decreased after staying at 1700 meters above sea level for three weeks (Schobersberger et al., 2003).

Hypoxic and metabolic syndromes

Obesity is no longer the time to imagine that Westerners are exclusive. Obesity has also been a social problem in Asian countries since 2000. When it comes to health, the proportion of being overweight or obese is higher than ever. As obesity increases the risk of metabolic diseases such as insulin resistance, hypertension, diabetes, cancer, cardiovascular disease and Obstructive sleep apnea (OSA), it begins to become a social concern and an economic burden on the country. OSA, which often occurs in obese people, not only increases the risk of cardiovascular diseases but also increases the risk of metabolic diseases. Intermittent apnea leads to a decrease in oxygen supply and aggravates the chronic inflammatory response of fat cells.

Nevertheless, recently, a critical study found that exposure to intermittent hypoxia reduces metabolic risk factors in obese patients. In other words, exposure to intermittent hypoxia can lose weight and therefore reduce metabolic risk factors. In fact, in the former Soviet Union, the hypoxia environment is very effective in relieving high blood pressure. Hypoxic environmental exposure has been reported as an effective intervention for weight loss. It is understood that according to this theoretical basis, a hypoxia exposure such as high altitude will increase the appetite-suppressing hormone Leptin (Loshbaugh et al., 2006), increase basal metabolic rate (BRM), and promote a decline in body fat (Pearce, Williams, Hamade, Chang, & White, 2006).

It is reported that hypoxic environment exposure can increase tissue oxygen supply, capillary density (Lecoultre et al., 2010), regulate the synthesis rate of mitochondria in skeletal muscle (Zoll et al., 2006), and promote the secretion of hormones related to energy metabolism, thus activating fat metabolism (Barnholt et al., 2006). At present, the mechanism of increased energy consumption during hypoxia exposure has not been fully identified, but it is believed that one of the main reasons is the activation of sympathetic nervous system (Louis & Punjabi, 2009; Mawson et al., 2000).

Exercise in hypoxic environment can promote mitochondrial biosynthesis, increase the process of fatty acid oxidation in muscle (Gilde & Van Bilsen, 2003; Zoll et al., 2006), increase the density of capillaries, the number and efficiency of muscle oxidase and mitochondria, thus activate fat metabolism (Lecoultre et al., 2010; Roels et al., 2007).

On the other hand, the increase of autonomic nervous activity under hypoxia environment, as an energy source, also proposes another possibility to promote the utilization of glucose and glycogen (Azevedo, Carey, Pories, Morris, & Dohm, 1995; Kelly et al., 2010). Hypoxia environment will increase the level of glutamate carrier protein GLUT-4, which not only promotes glucose metabolism but also may increase

insulin sensitivity (Chiu et al., 2004; Chou et al., 2004; Mackenzie, Maxwell, Castle, Brickley, & Watt, 2011). Another main reason for the decrease of body fat during intermittent hypoxia exposure is that the hypoxia environment activates the mechanism of inhibition of appetite center, increases the capacity of oxygen transport, and improves the transport and decomposition of fat energy sources; thus the possibility of activating sugar and fat metabolism was proposed (Camacho-Cardenosa et al., 2018; Wenger, 2002).

In addition, physical exercise in a hypoxic environment can achieve the effect of high-intensity exercise at sea level, even with lower intensity training at sea level (Camacho-Cardenosa et al., 2018). It may be the most suitable non-drug intervention for highly obese people, patients with skeletal muscle systems and the elderly who can only do low-intensity exercise.

Potential mechanism underlying reducing metabolic risk factors

The possibility that the hypoxia environment itself reduces the metabolic risk factors, that is, the possibility of weight loss in the hypoxia environment is largely due to loss of appetite and increased energy consumption, both of which can be predicted. Changes in hormones related to the appetite center do reduce appetite at an altitude of more than 5000 meters, but weight loss does not occur if they lose weight according to the subjects' appetite and eating habits. In particular, it is almost impossible to count on the weight loss effects of appetite inhibition when intermittently exposed to hypoxia at sea level. The regulation of energy intake and consumption is maintained by energy balance sensing mechanism. Therefore, a signal protein (AMP-activated protein kinase, AMPK) is considered to play an important role in the regulation of energy intake and consumption, which acts on the balance of energy intake and consumption. AMPK will respond to the increase or decrease in the production and consumption of ATP, especially when the ATP/ADP ratio decreases. The change in the proportion of

ATP/ADP can be adjusted in a reduced energy source or in a hypoxic environment. The general role of AMPK in the body is to participate in the decomposition of energy, rather than the synthesis or storage of metabolites. Another mechanism for activating AMPK includes IL-6-AMPK, hypoxia, which increases muscle IL-6 and increases IL-6 activation of AMPK. Several researchers have studied the hypoxic environment increases IL-6 not only in healthy people but also in patients with hypoxia (Mazzeo et al., 2001; Klausen et al., 1997). Lundby & Steensberg (2004) analyzed the effects of grade and chronic hypoxia environment on IL-6 increased by exercise and reported the synergistic effect of exercise and hypoxia environment. Under the relative intensity, the concentration of IL-6 was no different from that in hypoxia and normal oxygen environment, but the concentration of IL-6 was higher in hypoxia environment at the same absolute maximum downward exercise. AMPK activity is regulated by Adipokine, such as energy source, sugar, leptin and adiponectin. Muscle leptin and lipoprotein activate AMPK to increase fat metabolism. In particular, adiponectin in the liver can increase fat metabolism and inhibit sugar production.

Picon-Reategui et al. (1970) believe that the fasting blood glucose content, erythrocyte and plasma sugar content of the population at high altitude are lower than those in the plain. The experimental results on glucose tolerance of people at high altitude are also very inconsistent. Sawhney et al. (1986) reported that glucose tolerance decreased at 3500m and increased after glucose load. In the plateau for 14 days, both the plain population and the native plateau population were significantly higher than those in the plain control group, and the native population was the highest. The content of plasma insulin in the immigrant population was significantly higher than that in the native population, and both of them were higher than those in the plain population. That may be due to the simultaneous increase of anti-insulin hormones caused by hypoxia at high altitude, which interferes with an

adaptive change in the effect of insulin on glucose metabolism. However, the medical research team of Mount Qomolangma in the United States, at an altitude of 6300m, found that the blood sugar content of the members was quite stable and did not increase after glucose load. When the plasma insulin increased after glucose load, the serum glucose content was lower than the plain value.

The inconsistency of these results is likely to be related to many factors such as residence time at altitude, dietary composition (especially sugars) and whether the heat energy is balanced or not. The ability of people at high altitude to use glucose is greater than that of people in plain. In the plateau environment, the utilization rate of glucose is increased, and there is a glucose threshold in the surrounding tissue, which is necessary for glucose to enter the tissue from the blood for metabolism. The low width value of the population at high altitude may be one of the reasons for the enhancement of the utilization ability of sugar in the population at high altitude, and it is one of the manifestations of their adaptability to hypoxia. In animal experiments, Lui et al. (2015) found that high-altitude exercise training (~4,300 m) for 6–8 weeks significantly improved maximum oxygen consumption (VO₂max) in rat pups in low and high altitudes and that the degree of improvement was greater in rat pups in a high altitude than those in a low altitude. In contrast, there were no significant changes in rat pups that underwent exercise training at sea level. Recently, multiple studies have investigated the effects of such environmental and genetic characteristics on exercise capacity, such as VO₂max and glycometabolism(Dabelea, Knowler, & Pettitt, 2000) or metabolic ability(Boney, Verma, Tucker, & Vohr, 2005; Catalano et al., 2009).

Conclusions

Many studies have attempted to identify the reasons why athletes born, raised, and trained at sea level cannot

outperform athletes born, raised, and trained at high altitudes even with temporary elevation or enhancement of physical metabolism-related parameters induced by temporary high-altitude training. The failure to draw a consistent conclusion, however, may be mainly attributable to the differences in participant selection, altitude for training, intensity and duration of training at high altitude, and selected measurement variables. However, most of all, this is a result of assessing the outcomes of high-altitude training after living at a high altitude only temporarily. Nevertheless, studies examining people who have been born, grown, and trained at a high altitude over several generations are lacking.

Acknowledgments

This work was funded by the department of education of Zhejiang province Foundation(KYZ04Y18258).

References

- Aiken, C. E., & Ozanne, S. E. (2014). Transgenerational developmental programming. *Hum Reprod Update*, **20**(1), 63-75. doi:10.1093/humupd/dmt043
- Armellini, F., Zamboni, M., Robbi, R., Todesco, T., et al. (1997). The effects of high altitude trekking on body composition and resting metabolic rate. *Horm Metab Res*, **29**(9), 458-461. doi:10.1055/s-2007-979077
- Azevedo, J. L., Jr., Carey, J. O., Pories, W. J., Morris, P. G., & Dohm, G. L. (1995). Hypoxia stimulates glucose transport in insulin-resistant human skeletal muscle. *Diabetes*, **44**(6), 695-698. doi:10.2337/diab.44.6.695
- Barnholt, K. E., Hoffman, A. R., Rock, P. B., Muza, S. R., et al. (2006). Endocrine responses to acute and chronic high-altitude exposure (4,300 meters): modulating effects of caloric restriction. *Am J Physiol Endocrinol Metab*, **290**(6), E1078-1088. doi:10.1152/ajpendo.00449.2005

- Bayol, S. A., Macharia, R., Farrington, S. J., Simbi, B. H., & Stickland, N. C. (2009). Evidence that a maternal "junk food" diet during pregnancy and lactation can reduce muscle force in offspring. *Eur J Nutr*, **48**(1), 62-65. doi:10.1007/s00394-008-0760-5
- Bayol, S. A., Simbi, B. H., Bertrand, J. A., & Stickland, N. C. (2008). Offspring from mothers fed a 'junk food' diet in pregnancy and lactation exhibit exacerbated adiposity that is more pronounced in females. *J Physiol*, **586**(13), 3219-3230. doi:10.1113/jphysiol.2008.153817
- Benso, A., Broglio, F., Aimaretti, G., Lucatello, B., Lanfranco, F., Ghigo, E., & Grottoli, S. (2007). Endocrine and metabolic responses to extreme altitude and physical exercise in climbers. *Eur J Endocrinol*, **157**(6), 733-740. doi:10.1530/EJE-07-0355
- Bo, H., Zhang, Y., & Ji, L. L. (2010). Redefining the role of mitochondria in exercise: a dynamic remodeling. *Ann N Y Acad Sci*, **1201**, 121-128. doi:10.1111/j.1749-6632.2010.05618.x
- Boney, C. M., Verma, A., Tucker, R., & Vohr, B. R. (2005). Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics*, **115**(3), e290-296. doi:10.1542/peds.2004-1808
- Camacho-Cardenosa, A., Camacho-Cardenosa, M., Burtscher, M., Martinez-Guardado, I., Timon, R., Brazo-Sayavera, J., & Olcina, G. (2018). High-Intensity Interval Training in Normobaric Hypoxia Leads to Greater Body Fat Loss in Overweight/Obese Women than High-Intensity Interval Training in Normoxia. *Front Physiol*, **9**, 60. doi:10.3389/fphys.2018.00060
- Carraway, M. S., Suliman, H. B., Jones, W. S., Chen, C. W., Babiker, A., & Piantadosi, C. A. (2010). Erythropoietin activates mitochondrial biogenesis and couples red cell mass to mitochondrial mass in the heart. *Circ Res*, **106**(11), 1722-1730. doi:10.1161/CIRCRESAHA.109.214353
- Carter, L. G., Lewis, K. N., Wilkerson, D. C., Tobia, C. M., et al. (2012). Perinatal exercise improves glucose homeostasis in adult offspring. *Am J Physiol Endocrinol Metab*, **303**(8), E1061-1068. doi:10.1152/ajpendo.00213.2012
- Carter, L. G., Qi, N. R., De Cabo, R., & Pearson, K. J. (2013). Maternal Exercise Improves Insulin Sensitivity in Mature Rat Offspring. *Medicine and Science in Sports and Exercise*, **45**(5), 832-840. doi:10.1249/MSS.0b013e31827de953
- Catalano, P. M., Farrell, K., Thomas, A., Huston-Presley, L., Mencia, P., de Mouzon, S. H., & Amini, S. B. (2009). Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr*, **90**(5), 1303-1313. doi:10.3945/ajcn.2008.27416
- Chapman, R. F., Stray-Gundersen, J., & Levine, B. D. (1998). Individual variation in response to altitude training. *J Appl Physiol (1985)*, **85**(4), 1448-1456. doi:10.1152/jappl.1998.85.4.1448
- Chitra, L., & Boopathy, R. (2014). Altered mitochondrial biogenesis and its fusion gene expression is involved in the high-altitude adaptation of rat lung. *Respir Physiol Neurobiol*, **192**, 74-84. doi:10.1016/j.resp.2013.12.007
- Chiu, L. L., Chou, S. W., Cho, Y. M., Ho, H. Y., et al. (2004). Effect of prolonged intermittent hypoxia and exercise training on glucose tolerance and muscle GLUT4 protein expression in rats. *J Biomed Sci*, **11**(6), 838-846. doi:10.1007/BF02254369
- Chou, S. W., Chiu, L. L., Cho, Y. M., Ho, H. Y., Ivy, J. L., Ho, C. F., & Kuo, C. H. (2004). Effect of systemic hypoxia on GLUT4 protein expression in exercised rat heart. *Jpn J Physiol*, **54**(4), 357-363. doi:10.2170/jjphysiol.54.357
- Clapp, J. F., 3rd, & Capeless, E. L. (1990). Neonatal morphometrics after endurance exercise during pregnancy. *Am J Obstet Gynecol*, **163**(6 Pt 1), 1805-1811. doi:10.1016/0002-9378(90)90754-u
- Dabelea, D., Knowler, W. C., & Pettitt, D. J. (2000). Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. *J Matern Fetal Med*, **9**(1), 83-88.
- Demory, M. L., Boerner, J. L., Davidson, R., Faust, W.,

- Miyake, T., Lee, I., . . . Parsons, S. J. (2009). Epidermal growth factor receptor translocation to the mitochondria: regulation and effect. *J Biol Chem*, **284(52)**, 36592-36604. doi:10.1074/jbc.M109.000760
- Desplanches, D., Amami, M., Dupre-Aucouturier, S., Valdivieso, P., Schmutz, S., Mueller, M., . . . Fluck, M. (2014). Hypoxia refines plasticity of mitochondrial respiration to repeated muscle work. *Eur J Appl Physiol*, **114(2)**, 405-417. doi:10.1007/s00421-013-2783-8
- Desplanches, D., Hoppeler, H., Linossier, M. T., Denis, C., Claassen, H., Dormois, D., . . . Geyssant, A. (1993). Effects of training in normoxia and normobaric hypoxia on human muscle ultrastructure. *Pflugers Arch*, **425(3-4)**, 263-267. doi:10.1007/BF00374176
- Florian, M., Jankowski, M., & Gutkowska, J. (2010). Oxytocin increases glucose uptake in neonatal rat cardiomyocytes. *Endocrinology*, **151(2)**, 482-491. doi:10.1210/en.2009-0624
- Fusch, C., Gfrorer, W., Koch, C., Thomas, A., Grunert, A., & Moeller, H. (1996). Water turnover and body composition during long-term exposure to high altitude (4,900-7,600m). *J Appl Physiol (1985)*, **80(4)**, 1118-1125. doi:10.1152/jappl.1996.80.4.1118
- Ge, R. L., Chen, Q. H., Wang, L. H., Gen, D., Yang, P., Kubo, K., et al. (1994). Higher exercise performance and lower VO₂max in Tibetan than Han residents at 4,700 m altitude. *J Appl Physiol (1985)*, **77(2)**, 684-691. doi:10.1152/jappl.1994.77.2.684
- Geiser, J., Vogt, M., Billeter, R., Zuleger, C., Belforti, F., & Hoppeler, H. (2001). Training high--living low: changes of aerobic performance and muscle structure with training at simulated altitude. *Int J Sports Med*, **22(8)**, 579-585. doi:10.1055/s-2001-18521
- Geng, T. Y., Li, P., Okutsu, M., Yin, X. H., Kwek, J., Zhang, M., & Yan, Z. (2010). PGC-1 alpha plays a functional role in exercise-induced mitochondrial biogenesis and angiogenesis but not fiber-type transformation in mouse skeletal muscle. *American Journal of Physiology-Cell Physiology*, **298(3)**, C572-C579. doi:10.1152/ajpcell.00481.2009
- Gilbert, S. F. (2001). Ecological developmental biology: developmental biology meets the real world. *Dev Biol*, **233(1)**, 1-12. doi:10.1006/dbio.2001.0210
- Gilde, A. J., & Van Bilsen, M. (2003). Peroxisome proliferator-activated receptors (PPARs): regulators of gene expression in heart and skeletal muscle. *Acta Physiol Scand*, **178(4)**, 425-434. doi:10.1046/j.1365-201X.2003.01161.x
- Hahn, A. G., & Gore, C. J. (2001). The effect of altitude on cycling performance: a challenge to traditional concepts. *Sports Med*, **31(7)**, 533-557. doi:10.2165/00007256-200131070-00008
- Harris, A. L. (2002). Hypoxia--a key regulatory factor in tumour growth. *Nat Rev Cancer*, **2(1)**, 38-47. doi:10.1038/nrc704
- Hawley, J. A., & Lessard, S. J. (2008). Exercise training-induced improvements in insulin action. *Acta Physiol (Oxf)*, **192(1)**, 127-135. doi:10.1111/j.1748-1716.2007.01783.x
- Holloway, K. V., O'Gorman, M., Woods, P., Morton, J. P., et al. (2009). Proteomic investigation of changes in human vastus lateralis muscle in response to interval-exercise training. *Proteomics*, **9(22)**, 5155-5174. doi:10.1002/pmic.200900068
- Hood, D. A., Adhihetty, P. J., Colavecchia, M., Gordon, J. W., Irrcher, I., Joseph, A. M., . . . Rungi, A. A. (2003). Mitochondrial biogenesis and the role of the protein import pathway. *Med Sci Sports Exerc*, **35(1)**, 86-94. doi:10.1097/00005768-200301000-00015
- Hoppeler, H., Klossner, S., & Vogt, M. (2008). Training in hypoxia and its effects on skeletal muscle tissue. *Scand J Med Sci Sports*, **18 (S1)**, 38-49. doi:10.1111/j.1600-0838.2008.00831.x
- Irrcher, I., Adhihetty, P. J., Joseph, A. M., Ljubicic, V., & Hood, D. A. (2003). Regulation of mitochondrial

- biogenesis in muscle by endurance exercise. *Sports Med*, **33(11)**, 783-793. doi:10.2165/00007256-200333110-00001
- Johnson, M. L., Robinson, M. M., & Nair, K. S. (2013). Skeletal muscle aging and the mitochondrion. *Trends in Endocrinology and Metabolism*, **24(5)**, 247-256. doi:10.1016/j.tem.2012.12.003
- Kalisiak, B., & Spitznagle, T. (2009). What effect does an exercise program for healthy pregnant women have on the mother, fetus, and child? *PM R*, **1(3)**, 261-266. doi:10.1016/j.pmrj.2008.12.006
- Kayser, B., & Verges, S. (2013). Hypoxia, energy balance and obesity: from pathophysiological mechanisms to new treatment strategies. *Obes Rev*, **14(7)**, 579-592. doi:10.1111/obr.12034
- Kelly, K. R., Williamson, D. L., Fealy, C. E., Kriz, D. A., Krishnan, R. K., Huang, H., . . . Kirwan, J. P. (2010). Acute altitude-induced hypoxia suppresses plasma glucose and leptin in healthy humans. *Metabolism*, **59(2)**, 200-205. doi:10.1016/j.metabol.2009.07.014
- Klausen, T., Olsen, N.V., Poilsen, T.D., Richalet, J.P., Pedersen, B.K.(1997). Hypoxemia increases serum interleukin-6 in humans. *Eur J Appl Physiol Occup Physiol*, **76(5)**, 480-482. doi: 10.1007/s004210050278
- Lanza, I. R., & Nair, K. S. (2009). Muscle mitochondrial changes with aging and exercise. *Am J Clin Nutr*, **89(1)**, 467S-471S. doi:10.3945/ajcn.2008.26717D
- Lecoultre, V., Boss, A., Tappy, L., Borrani, F., Tran, C., Schneiter, P., & Schutz, Y. (2010). Training in hypoxia fails to further enhance endurance performance and lactate clearance in well-trained men and impairs glucose metabolism during prolonged exercise. *Exp Physiol*, **95(2)**, 315-330. doi:10.1113/expphysiol.2009.050690
- Lehman, J. J., Barger, P. M., Kovacs, A., Saffitz, J. E., Medeiros, D. M., & Kelly, D. P. (2000). Peroxisome proliferator-activated receptor gamma coactivator-1 promotes cardiac mitochondrial biogenesis. *J Clin Invest*, **106(7)**, 847-856. doi:10.1172/JCI10268
- Levett, D. Z., Radford, E. J., Menassa, D. A., Graber, E. F., et al. (2012). Acclimatization of skeletal muscle mitochondria to high-altitude hypoxia during an ascent of Everest. *FASEB J*, **26(4)**, 1431-1441. doi:10.1096/fj.11-197772
- Levine, B. D. (2002). Intermittent hypoxic training: fact and fancy. *High Alt Med Biol*, **3(2)**, 177-193. doi:10.1089/15270290260131911
- Levine, B. D., & Stray-Gundersen, J. (1997). "Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance. *J Appl Physiol (1985)*, **83(1)**, 102-112. doi:10.1152/jappl.1997.83.1.102
- Levine, B. D., & Stray-Gundersen, J. (2001). The effects of altitude training are mediated primarily by acclimatization, rather than by hypoxic exercise. *Adv Exp Med Biol*, **502**, 75-88. doi:10.1007/978-1-4757-3401-0_7
- Lin, J., Handschin, C., & Spiegelman, B. M. (2005). Metabolic control through the PGC-1 family of transcription coactivators. *Cell metabolism*, **1(6)**, 361-370. doi: 10.1016/j.cmet.2005.05.004
- Lin, J., Wu, H., Tarr, P. T., Zhang, C. Y., et al. (2002). Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature*, **418(6899)**, 797-801. doi:10.1038/nature00904
- Little, J. P., Safdar, A., Bishop, D., Tarnopolsky, M. A., & Gibala, M. J. (2011). An acute bout of high-intensity interval training increases the nuclear abundance of PGC-1alpha and activates mitochondrial biogenesis in human skeletal muscle. *Am J Physiol Regul Integr Comp Physiol*, **300(6)**, R1303-1310. doi:10.1152/ajpregu.00538.2010
- Loshbaugh, J. E., Loeppky, J. A., & Greene, E. R. (2006). Effects of acute hypobaric hypoxia on resting and postprandial superior mesenteric artery blood flow. *High Alt Med Biol*, **7(1)**, 47-53. doi:10.1089/ham.2006.7.47
- Louis, M., & Punjabi, N. M. (2009). Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. *J Appl Physiol (1985)*, **106(5)**, 1538-1544. doi:10.1152/japplphysiol.91523.

- 2008
- Lui, M. A., Mahalingam, S., Patel, P., Connaty, A. D., et al. (2015). High-altitude ancestry and hypoxia acclimation have distinct effects on exercise capacity and muscle phenotype in deer mice. *Am J Physiol Regul Integr Comp Physiol*, **308**(9), R779-791. doi:10.1152/ajpregu.00362.2014
- Lundby, C., Calbet, J. A., & Robach, P. (2009). The response of human skeletal muscle tissue to hypoxia. *Cell Mol Life Sci*, **66**(22), 3615-3623. doi:10.1007/s00018-009-0146-8
- Lundby, C., & Steensberg, A. (2004). Interleukin-6 response to exercise during acute and chronic hypoxia. *Eur J Appl Physiol*, **91**(1), 88-93. doi:10.1007/s00421-003-0935-y
- MacInnis, M. J., & Rupert, J. L. (2011). 'ome on the Range: altitude adaptation, positive selection, and Himalayan genomics. *High Alt Med Biol*, **12**(2), 133-139. doi:10.1089/ham.2010.1090
- Mackenzie, R., Maxwell, N., Castle, P., Brickley, G., & Watt, P. (2011). Acute hypoxia and exercise improve insulin sensitivity (S(I) (2*)) in individuals with type 2 diabetes. *Diabetes Metab Res Rev*, **27**(1), 94-101. doi:10.1002/dmrr.1156
- Major, G. C., & Doucet, E. (2004). Energy intake during a typical Himalayan trek. *High Alt Med Biol*, **5**(3), 355-363. doi:10.1089/1527029042002907
- Mawson, J. T., Braun, B., Rock, P. B., Moore, L. G., Mazzeo, R., & Butterfield, G. E. (2000). Women at altitude: energy requirement at 4,300 m. *J Appl Physiol (1985)*, **88**(1), 272-281. doi:10.1152/jappl.2000.88.1.272
- Mazzeo, R.S., Donovan, Fleshner, D., Butterfield, G.E., Zamudio, S., Wolfel, E.E., Moore, L.G.(2001). Interleukin-6 response to exercise and high-altitude exposure: influence of alpha-adrenergic blockade. *J Appl Physiol(1985)*, **91**(5), 2143-2149. doi: 10.1152/jappl.2001.91.5.2143
- Meisinger, C., Sickmann, A., & Pfanner, N. (2008). The mitochondrial proteome: from inventory to function. *Cell*, **134**(1), 22-24. doi:10.1016/j.cell.2008.06.043
- Melissa, L., MacDougall, J. D., Tarnopolsky, M. A., Cipriano, N., & Green, H. J. (1997). Skeletal muscle adaptations to training under normobaric hypoxic versus normoxic conditions. *Med Sci Sports Exerc*, **29**(2), 238-243. doi:10.1097/00005768-199702000-00012
- Michiels, C. (2004). Physiological and pathological responses to hypoxia. *Am J Pathol*, **164**(6), 1875-1882. doi:10.1016/S0002-9440(10)63747-9
- Miura, S., Tomitsuka, E., Kamei, Y., Yamazaki, T., et al. (2006). Overexpression of peroxisome proliferator-activated receptor gamma co-activator-1alpha leads to muscle atrophy with depletion of ATP. *Am J Pathol*, **169**(4), 1129-1139. doi:10.2353/ajpath.2006.060034
- Moore, L. G., Shriver, M., Bemis, L., Hickler, B., et al. (2004). Maternal adaptation to high-altitude pregnancy: an experiment of nature--a review. *Placenta*, **25**, S60-S71. doi:10.1016/j.placenta.2004.01.008
- Moret, P., Covarrubias, E., & Coudert, J. (1971). [Adaptation of coronary circulation and metabolism of the myocardium to chronic hypoxia of high altitudes]. *Arch Mal Coeur Vaiss*, **64**(10), 1424-1430.
- Mousseau, T. A., & Fox, C. W. (1998). The adaptive significance of maternal effects. *Trends Ecol Evol*, **13**(10), 403-407. doi:10.1016/s0169-5347(98)01472-4
- Murray, A. J. (2009). Metabolic adaptation of skeletal muscle to high altitude hypoxia: how new technologies could resolve the controversies. *Genome Med*, **1**(12), 117. doi:10.1186/gm117
- Newgard, C. B., Hwang, P. K., & Fletterick, R. J. (1989). The family of glycogen phosphorylases: structure and function. *Crit Rev Biochem Mol Biol*, **24**(1), 69-99. doi:10.3109/10409238909082552
- Ng, S. F., Lin, R. C., Laybutt, D. R., Barres, R., Owens, J. A., & Morris, M. J. (2010). Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. *Nature*, **467**(7318), 963-966. doi:10.1038/

- nature09491
- Patti, M. E. (2013). Intergenerational programming of metabolic disease: evidence from human populations and experimental animal models. *Cell Mol Life Sci*, **70(9)**, 1597-1608. doi:10.1007/s00018-013-1298-0
- Pearce, W. J., Williams, J. M., Hamade, M. W., Chang, M. M., & White, C. R. (2006). Chronic hypoxia modulates endothelium-dependent vasorelaxation through multiple independent mechanisms in ovine cranial arteries. *Adv Exp Med Biol*, **578**, 87-92. doi:10.1007/0-387-29540-2_14
- Peixoto-Silva, N., Frantz, E. D., Mandarim-de-Lacerda, C. A., & Pinheiro-Mulder, A. (2011). Maternal protein restriction in mice causes adverse metabolic and hypothalamic effects in the F1 and F2 generations. *Br J Nutr*, **106(9)**, 1364-1373. doi:10.1017/S0007114511001735
- Picon-Reategui, E., Buskirk, E. R., & Baker, P. T. (1970). Blood glucose in high-altitude natives and during acclimatization to altitude. *J Appl Physiol*, **29(5)**, 560-563. doi:10.1152/jappl.1970.29.5.560
- Pilegaard, H., Saltin, B., & Neufer, P. D. (2003). Exercise induces transient transcriptional activation of the PGC-1 α gene in human skeletal muscle. *J Physiol*, **546(Pt 3)**, 851-858. doi:10.1113/jphysiol.2002.034850
- Pinto, M. L., & Shetty, P. S. (1995). Influence of exercise-induced maternal stress on fetal outcome in Wistar rats: inter-generational effects. *Br J Nutr*, **73(5)**, 645-653. doi:10.1079/bjn19950070
- Roels, B., Thomas, C., Bentley, D. J., Mercier, J., Hayot, M., & Millet, G. (2007). Effects of intermittent hypoxic training on amino and fatty acid oxidative combustion in human permeabilized muscle fibers. *J Appl Physiol (1985)*, **102(1)**, 79-86. doi:10.1152/jappphysiol.01319.2005
- Santos, J. L., Perez-Bravo, F., Carrasco, E., Calvillan, M., & Albala, C. (2001). Low prevalence of type 2 diabetes despite a high average body mass index in the Aymara natives from Chile. *Nutrition*, **17(4)**, 305-309. doi:10.1016/s0899-9007(00)00551-7
- Sawhney, R. C., Malhotra, A. S., Singh, T., Rai, R. M., & Sinha, K. C. (1986). Insulin secretion at high altitude in man. *International journal of biometeorology*, **30(3)**, 231-238. doi:10.1007/BF02189466
- Schena, F., Guerrini, F., Tregnaghi, P., & Kayser, B. (1992). Branched-chain amino acid supplementation during trekking at high altitude. The effects on loss of body mass, body composition, and muscle power. *Eur J Appl Physiol Occup Physiol*, **65(5)**, 394-398. doi:10.1007/BF00243503
- Schobersberger, W., Schmid, P., Lechleitner, M., von Duvillard, S. P., et al. (2003). Austrian Moderate Altitude Study 2000 (AMAS 2000). The effects of moderate altitude (1,700 m) on cardiovascular and metabolic variables in patients with metabolic syndrome. *Eur J Appl Physiol*, **88(6)**, 506-514. doi:10.1007/s00421-002-0736-8
- Semenza, G. L. (1998). Hypoxia-inducible factor 1: master regulator of O₂ homeostasis. *Curr Opin Genet Dev*, **8(5)**, 588-594. doi:10.1016/s0959-437x(98)80016-6
- Sherpa, L. Y., Deji, Stigum, H., Chongsuvivatwong, V., Thelle, D. S., & Bjertness, E. (2010). Obesity in Tibetans aged 30-70 living at different altitudes under the north and south faces of Mt. Everest. *Int J Environ Res Public Health*, **7(4)**, 1670-1680. doi:10.3390/ijerph7041670
- Short, K. R., Nair, K. S., & Stump, C. S. (2004). Impaired mitochondrial activity and insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med*, **350(23)**, 2419-2421. doi:10.1056/NEJM200406033502320
- Sun, S. F., Droma, T. S., Zhang, J. G., Tao, J. X., et al. (1990). Greater maximal O₂ uptakes and vital capacities in Tibetan than Han residents of Lhasa. *Respiration physiology*, **79(2)**, 151-161. doi:10.1016/0034-5687(90)90015-q
- Susser, E., Kirkbride, J. B., Heijmans, B. T., Kresovich,

- J. K., Lumey, L. H., & Stein, A. D. (2012). Maternal Prenatal Nutrition and Health in Grandchildren and Subsequent Generations. *Annual Review of Anthropology*, **41**, 577-610. doi:10.1146/annurev-anthro-081309-145645
- Taylor, E. R., Hurrell, F., Shannon, R. J., Lin, T. K., Hirst, J., & Murphy, M. P. (2003). Reversible glutathionylation of complex I increases mitochondrial superoxide formation. *J Biol Chem*, **278(22)**, 19603-19610. doi:10.1074/jbc.M209359200
- Terada, S., & Tabata, I. (2004). Effects of acute bouts of running and swimming exercise on PGC-1alpha protein expression in rat epitrochlearis and soleus muscle. *Am J Physiol Endocrinol Metab*, **286(2)**, E208-216. doi:10.1152/ajpendo.00051.2003
- Terrados, N., Jansson, E., Sylven, C., & Kaijser, L. (1990). Is hypoxia a stimulus for synthesis of oxidative enzymes and myoglobin? *J Appl Physiol* (1985), **68(6)**, 2369-2372. doi:10.1152/jappl.1990.68.6.2369
- Uller, T. (2008). Developmental plasticity and the evolution of parental effects. *Trends Ecol Evol*, **23(8)**, 432-438. doi:10.1016/j.tree.2008.04.005
- Vogt, M., & Hoppeler, H. (2010). Is hypoxia training good for muscles and exercise performance? *Prog Cardiovasc Dis*, **52(6)**, 525-533. doi:10.1016/j.pcad.2010.02.013
- Vogt, M., Puntchart, A., Geiser, J., Zuleger, C., Billeter, R., & Hoppeler, H. (2001). Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. *J Appl Physiol* (1985), **91(1)**, 173-182. doi:10.1152/jappl.2001.91.1.173
- Weitz, C. A., Liu, J. C., He, X., Chin, C. T., & Garruto, R. M. (2013). Responses of Han migrants compared to Tibetans at high altitude. *Am J Hum Biol*, **25(2)**, 169-178. doi:10.1002/ajhb.22368
- Wenger, R. H. (2002). Cellular adaptation to hypoxia: O₂-sensing protein hydroxylases, hypoxia-inducible transcription factors, and O₂-regulated gene expression. *FASEB journal*, **16(10)**, 1151-1162. doi:10.1096/fj.01-0944rev
- Wu, T. Y., Ding, S. Q., Liu, J. L., Yu, M. T., et al. (2007). Who should not go high: chronic disease and work at altitude during construction of the Qinghai-Tibet railroad. *High Alt Med Biol*, **8(2)**, 88-107. doi:10.1089/ham.2007.1015
- Wu, Z., Puigserver, P., Andersson, U., Zhang, C., Adelmant, G., Mootha, V., Spiegelman, B. M. (1999). Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell*, **98(1)**, 115-124. doi:10.1016/S0092-8674(00)80611-X
- Yang, D., Peng, Y., Ouzhuluobu, Bianbazhuoma, et al. (2016). HMOX2 Functions as a Modifier Gene for High-Altitude Adaptation in Tibetans. *Human mutation*, **37(2)**, 216-223. doi:10.1002/humu.22935
- Zoll, J., Steiner, R., Meyer, K., Vogt, M., Hoppeler, H., & Fluck, M. (2006). Gene expression in skeletal muscle of coronary artery disease patients after concentric and eccentric endurance training. *Eur J Appl Physiol*, **96(4)**, 413-422. doi:10.1007/s00421-005-0082-8