



FACULTAT DE BIOLOGIA
DEPARTAMENT DE FISIOLOGIA

“HIPÒXIA HIPOBÀRICA
INTERMITENT: APORTACIÓ PERIFÈRICA D’OXIGEN I
INDICADORS DEL METABOLISME MUSCULAR”

Memòria presentada per **Pere Panisello Tafalla** per optar al Grau de
Doctor per la Universitat de Barcelona

Tesi realitzada sota la direcció del Dr. Ginés Viscor i Carrasco i del Dr. Joan Ramon Torrella i Guió del Departament de Fisiologia de Biologia. Adscrita al Departament de Fisiologia, Facultat de Biologia, Universitat de Barcelona, programa Fisiologia (Bienni 2001-2003)

Ginés Viscor i Carrasco

Joan Ramon Torrella i Guió

Pere Panisello i Tafalla

Barcelona, 2006

8 BIBLIOGRAFIA

8 Bibliografia

- Abdelmalki, A., Fimbel, S., MayetSornay, M. H., Sempore, B., & Favier, R. 1996. Aerobic capacity and skeletal muscle properties of normoxic and hypoxic rats in response to training. *Pflugers Archiv-European Journal of Physiology* 431:671-679.
- Alegret, J. M., Vinolas, X., Palazon, O., Vernis, J. M., Ferrer, A., & Oter, R. 2000. [Intermittent pre-excitation after adenosine administration]. *Rev.Esp.Cardiol* 53:1132-1135.
- Asemu, G., Papousek, F., Ostadal, B., & Kolar, F. 1999. Adaptation to high altitude hypoxia protects the rat heart against ischemia-induced arrhythmias. Involvement of mitochondrial K(ATP) channel. *J Mol.Cell Cardiol.* 31:1821-1831.
- Anderson, G. L. & Bullard, R. W. 1971. Effect of High Altitude on Lactic Dehydrogenase Isozymes and Anoxic Tolerance of Rat Myocardium. *Proceedings of the Society for Experimental Biology and Medicine* 138:441-&.
- Askew, E. W. 2002. Work at high altitude and oxidative stress: antioxidant nutrients. *Toxicology* 180:107-119.
- Axelson, H., Fredlund, E., Ovenberger, M., Landberg, G., & Pahlman, S. 2005. Hypoxia-induced dedifferentiation of tumor cells - A mechanism behind heterogeneity and aggressiveness of solid tumors. *Seminars in Cell & Developmental Biology* 16:554-563.
- Bailey, D. M., Davies, B., & Baker, J. 2000. Training in hypoxia: modulation of metabolic and cardiovascular risk factors in men. *Med.Sci.Sports Exerc* 32:1058-1066.
- Bailey, D. M., Davies, B., & Young, I. S. 2001. Intermittent hypoxic training: implications for lipid peroxidation induced by acute normoxic exercise in active men. *Clinical Science* 101:465-475.
- Banchero, N. 1987. Cardiovascular responses to chronic hypoxia. *Annu.Rev.Physiol* 49:465-476.
- Banchero, N., Van, B. M., & Smith, S. L. 1987. Ventricular weights in guinea pigs acclimated to cold plus hypoxia. *Proc.Soc.Exp.Biol.Med* 186:36-40.
- Bärtsch, P., Maggiorini, M., & Swenson, ER. 2003. Update on high altitude pulmonary edema. En "Health and Height" C.Leal, A. Ricart G. Viscor (Eds). Publicaciones de la Universitat de Barcelona. 23-29.
- Bass, A., Ostadal, B., Prochazka, J., Pelouch, V., Samanek, M., & Stejskalova, M. 1989. Intermittent high altitude--induced changes in energy metabolism in the rat myocardium and their reversibility. *Physiol Bohemoslov* 38:155-161.
- Baumgartner, RW. 2003. The Brain at High Altitude. En "Health and Height" C.Leal, A. Ricart G. Viscor (Eds). Publicaciones de la Universitat de Barcelona. 163-172.
- Bender, P. R., Tucker, A., & Twietmeyer, T. A. 1984. Skeletal-Muscle Capillarity During Recovery from Chronic Hypoxic Exposure. *Microcirculation Endothelium and Lymphatics* 1:71-85.
- Beutler E, Blume KG, Kaplan JC, Lohr GW, Ramot B, Valentine WN. 1977. International Committee for Standardization in Haematology: recommended methods for red-cell enzyme analysis. *Br.J.Haematol* 35:331-340.

- Bigard, A. X., Brunet, A., Guezennec, C. Y., & Monod, H. 1991. Skeletal-Muscle Changes After Endurance Training at High-Altitude. *Journal of Applied Physiology* 71:2114-2121.
- Bigard, A. X., Brunet, A., Serrurier, B., Guezennec, C. Y., & Monod, H. 1992. Effects of Endurance Training at High-Altitude on Diaphragm Muscle Properties. *Pflugers Archiv-European Journal of Physiology* 422:239-244.
- Bottinelli, R., Schiaffino, S., & Reggiani, C. 1991. Force-velocity relations and myosin heavy chain isoform compositions of skinned fibres from rat skeletal muscle. *J Physiol* 437:655-672.
- Bradford, M. M. 1976. Rapid and Sensitive Method for Quantitation of Microgram Quantities of Protein Utilizing Principle of Protein-Dye Binding. *Analytical Biochemistry* 72:248-254.
- Brooke, M. H. & Kaiser, K. K. 1970. Muscle Fiber Types - How Many and What Kind. *Archives of Neurology* 23:369-379.
- Brunori, M. 2001a. Nitric oxide moves myoglobin centre stage. *Trends in Biochemical Sciences* 26:209-210.
- Brunori, M. 2001b. Nitric oxide, cytochrome-c oxidase and myoglobin. *Trends in Biochemical Sciences* 26:21-23.
- Bunn, H. F. & R. O. Poyton. 1996. Oxygen sensing and molecular adaptation to hypoxia. *Physiol Rev* 76: 839-885.
- Bunn, H. F., J. Gu, L. E. Huang, J. W. Park, & H. Zhu. 1998. Erythropoietin: a model system for studying oxygen-dependent gene regulation. *Journal of Experimental Biology* 201: 1197-1201.
- Burke, R. E., Levine, D. N., & Zajac, F. E., III 1971. Mammalian motor units: physiological-histochemical correlation in three types in cat gastrocnemius. *Science* 174:709-712.
- Burke, R. E., Levine, D. N., Tsairis, P., & Zajac, F. E., III 1973. Physiological types and histochemical profiles in motor units of the cat gastrocnemius. *J Physiol* 234:723-748.
- Burke, R. E., Levine, D. N., Salcman, M., & Tsairis, P. 1974. Motor units in cat soleus muscle: physiological, histochemical and morphological characteristics. *J Physiol* 238:503-514.
- Burmester, T. & Hankeln, T. 2004. Neuroglobin: a respiratory protein of the nervous system. *News Physiol Sci* 19:110-113.
- Carmeliet, P. 2005a. Angiogenesis in life, disease and medicine. *Nature* 438:932-936.
- Carmeliet, P. 2005b. VEGF as a key mediator of angiogenesis in cancer. *Oncology* 69:4-10.
- Casas, H., Murtra, B., Casas, M., Ibanez, J., Ventura, J. L., Ricart, A., Rodriguez, F., Viscor, G., Palacios, L., Pages, T., & Rama, R. 2001. Increased blood ammonia in hypoxia during exercise in humans. *Journal of Physiology and Biochemistry* 57:303-312.

- Casas, M., Casas, H., Pages, T., Rama, R., Ricart, A., Ventura, J. L., Ibanez, J., Rodriguez, F. A., & Viscor, G. 2000. Intermittent hypobaric hypoxia induces altitude acclimation and improves the lactate threshold. *Aviation Space and Environmental Medicine* 71:125-130.
- Cassin, S., Gilbert, R. D., Bunnell, C. E., & Johnson, E. M. 1971. Capillary Development During Exposure to Chronic Hypoxia. *American Journal of Physiology* 220:448.
- Carretelli, P. & Samaja, M. 2003. Acid-base balance at exercise in normoxia and in chronic hypoxia. Revisiting the "lactate paradox". *Eur.J Appl.Physiol* 90:431-448.
- Clanton, T. L. & Klawitter, P. F. 2001. Physiological and genomic consequences of intermittent hypoxia - Invited Review: Adaptive responses of skeletal muscle to intermittent hypoxia: the known and the unknown. *J Appl. Physiol* 90:2476-2487.
- Clark, D. R. & Smith, P. 1978. Capillary Density and Muscle-Fiber Size in the Hearts of Rats Subjected to Simulated High-Altitude. *Cardiovascular Research* 12:578-584.
- Clarke, C. & Duff, J. 1976. Mountain Sickness, Retinal Hemorrhages, and Acclimatization on Mount Everest in 1975. *British Medical Journal* 2:495-497.
- Cobb, M. A., Schutt, W. A., & Hermanson, J. W. 1994. Morphological, Histochemical, and Myosin Isoform Analysis of the Diaphragm of Adult Horses, *Equus-Caballus*. *Anatomical Record* 238:317-325.
- Corno, A. F., Milano, G., Samaja, M., Tozzi, P., & von Segesser, L. K. 2002. Chronic hypoxia: a model for cyanotic congenital heart defects. *J Thorac.Cardiovasc.Surg* 124:105-112.
- Daneshrad, Z., Garcia-Riera, M. P., Verdys, M., & Rossi, A. 2000. Differential responses to chronic hypoxia and dietary restriction of aerobic capacity and enzyme levels in the rat myocardium. *Molecular and Cellular Biochemistry* 210:159-166.
- Daneshrad, Z., Verdys, M., Birot, O., Troff, F., Bigard, A. X., & Rossi, A. 2003. Chronic hypoxia delays myocardial lactate dehydrogenase maturation in young rats. *Experimental Physiology* 88:405-413.
- Deindl, E., Kolar, F., Neubauer, E., Vogel, S., Schaper, W., & Ostadal, B. 2003. Effect of intermittent high altitude hypoxia on gene expression in rat heart and lung. *Physiological Research* 52:147-157.
- Desplanches, D., Hoppeler, H., Linossier, M. T., Denis, C., Claassen, H., Dormois, D., Lacour, J. R., & Geysant, A. 1993. Effects of Training in Normoxia and Normobaric Hypoxia on Human Muscle Ultrastructure. *Pflugers Archiv-European Journal of Physiology* 425:263-267.
- Desplanches, D., Hoppeler, H., Tuscher, L., Mayet, M. H., Spielvogel, H., Ferretti, G., Kayser, B., Leuenberger, M., Grunenfelder, A., & Favier, R. 1996. Muscle tissue adaptations of high-altitude natives to training in chronic hypoxia or acute normoxia. *J Appl.Physiol* 81:1946-1951.
- Desplanches, D. 1997. Structural and functional adaptations of skeletal muscle to weightlessness. *Int.J Sports Med.* 18 Suppl 4:S259-S264.
- Detroyer, A. & Estenne, M. 1988. Functional-Anatomy of the Respiratory Muscles. *Clinics in Chest Medicine* 9:175-193.

- Deveci, D., Marshall, J. M., & Egginton, S. 2002. Chronic hypoxia induces prolonged angiogenesis in skeletal muscles of rat. *Experimental Physiology* 87:287-291.
- Eby, S. H. & Banchemo, N. 1976. Capillary density of skeletal muscle in Andean dogs. *Proc.Soc.Exp.Biol.Med* 151:795-798.
- Eckardt, K. U. & Bauer, C. 1989. Erythropoietin in health and disease. *Eur.J Clin.Invest* 19:117-127.
- Ehrenbourg, I.V., & Kondrykinskaya, I.I. 1993. The efficiency of interval hypoxic training in therapy of chronic obstructive pulmonary diseases. *Hyp. Med. J* 1: 1: 17-18.
- Ehrenburg, I.V., Starkova, N.T., Davydov, A.L., & Tkatchouk, E.N. 2001. Effects of interval hypoxic therapy in non-insulin dependent diabetes mellitus (NIDDM). Double blind placebo controlled study. *High Altitude Medicine & Biology* Spring 2: 1: 105.
- Ehrenreich, H. & Siren, A. L. 2001. Neuroprotection--what does it mean?--What means do we have? *Eur.Arch.Psychiatry Clin.Neurosci* 251:149-151.
- Ehrenreich, H., Hasselblatt, M., Dembowski, C., Cepek, L., Lewczuk, P., Stiefel, M., Rustenbeck, H. H., Breiter, N., Jacob, S., Knerlich, F., Bohn, M., Poser, W., Ruther, E., Kochen, M., Gefeller, O., Gleiter, C., Wessel, T. C., De, R. M., Itri, L., Prange, H., Cerami, A., Brines, M., & Siren, A. L. 2002. Erythropoietin therapy for acute stroke is both safe and beneficial. *Mol.Med* 8:495-505.
- Ehrenreich, H., Degner, D., Meller, J., Brines, M., Behe, M., Hasselblatt, M., Woldt, H., Falkai, P., Knerlich, F., Jacob, S., von Ahsen, N., Maier, W., Bruck, W., Ruther, E., Cerami, A., Becker, W., & Siren, A. L. 2004. Erythropoietin: a candidate compound for neuroprotection in schizophrenia. *Molecular Psychiatry* 9:42-54.
- Essen-Gustavsson, B. & Henriksson, J. 1984. Enzyme levels in pools of microdissected human muscle fibres of identified type. Adaptive response to exercise. *Acta Physiol Scand* 120:505-515.
- Fedorova, O.V., Tsvetkova, A.M., Tkatchouk, E.N. 2003. Role of interval hypoxic training in the treatment of obesity. *Hyp. Med. J* 11: 4: 58-62.
- Ferrara, N. 2005. VEGF as a therapeutic target in cancer. *Oncology* 69:11-16.
- Ferrara, N. & Kerbel, R. S. 2005. Angiogenesis as a therapeutic target. *Nature* 438:967-974.
- Ferretti, G., Boutellier, U., Pendergast, D. R., Moia, C., Minetti, A. E., Howald, H., & di Prampero, P. E. 1990. Oxygen transport system before and after exposure to chronic hypoxia. *Int.J Sports Med* 11 Suppl 1:S15-S20.
- Fischer, R. 2003 Respiratory pathologies in the mountain- How high can people go?. En "Health and Height" C.Leal, A. Ricart G. Viscor (Eds). Publicaciones de la Universitat de Barcelona 75-79.
- Fliss, H., Comas, T.M., Ehrenburg, I.V., Gulyaeva N.V., Tkatchouk, E.N. 1997. Effects of in vivo hypoxic preconditioning on transcription factors in rat heart. *Hyp. Med. J* 5: 3: 9-10.
- Flogel, U., Merx, M. W., Godecke, A., Decking, U. K. M., & Schrader, J. 2001. Myoglobin: A scavenger of bioactive NO. *Proceedings of the National Academy of Sciences of the United States of America* 98:735-740.

- Folkman, J. 1995a. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat.Med* 1:27-31.
- Folkman, J. 1995b. Angiogenesis inhibitors generated by tumors. *Mol.Med.* 1:120-122.
- Fouces, V., Torrella, J. R., Palomeque, J., & Viscor, G. 1993. A Histochemical Atpase Method for the Demonstration of the Muscle Capillary Network. *Journal of Histochemistry & Cytochemistry* 41:283-289.
- Garry, D.J., Garry, M.G., Richardson, J.A., Williams, S.C., Mammen P.P., Shelton, J.M., & Goetsch, S.C. 2002. Neuroglobin, a novel member of the globin family, is expressed in focal regions of the brain. *J Histochem Cytochem* Dec 50:12:1591-1598.
- Garry, D. J. & Mammen, P. P. A. 2003. Neuroprotection and the role of neuroglobin. *Lancet* 362:342-343.
- Garry, D. J., Kanatous, S. B., & Mammen, P. P. A. 2003. Emerging roles for myoglobin in the heart. *Trends in Cardiovascular Medicine* 13:111-116.
- Ge Ri-Li, Helum Gaowa, Jin Guo-en, & Yang Ying-Zhong. 2003. High-altitude Heart Disease in Qinghai-Tibert. En "Health and Height" C.Leal, A. Ricart G. Viscor (Eds) Publicaciones de la Universitat de Barcelona.197-204.
- Gibbs, JS., & Galliford, J. 2003. Cardiovascular Disease at High Altitude. En "Health and Height" C.Leal, A. Ricart G. Viscor (Eds). Publicaciones de la Universitat de Barcelona 181-186.
- Gold, A. J. & Costello, L. C. 1974. Effects of Altitude and Semi-Starvation on Heart Mitochondrial-Function. *American Journal of Physiology* 227:1336-1339.
- Green, H. J., Plyley, M. J., Smith, D. M., & Kile, J. G. 1989. Extreme Endurance Training and Fiber Type Adaptation in Rat Diaphragm. *Journal of Applied Physiology* 66:1914-1920.
- Guth, L. & Samaha, F. J. 1970. Procedure for the histochemical demonstration of actomyosin ATPase. *Exp.Neurol* 28:365-367.
- Hackett, PH. 2003. Acute Mountain Sickness and High Altitude Cerebral Edema: a Review for the Practitioner. En "Health and Height" C.Leal, A. Ricart G. Viscor (Eds) Publicaciones de la Universitat de Barcelona 9-22.
- Hansen, G., Martinuk, K. J. B., Bell, G. J., MacLean, I. M., Martin, T. P., & Putman, C. T. 2004. Effects of spaceflight on myosin heavy-chain content, fibre morphology and succinate dehydrogenase activity in rat diaphragm. *Pflugers Archiv-European Journal of Physiology* 448:239-247.
- Harris, A. L. 2002. Hypoxia - A key regulatory factor in tumour growth. *Nature Reviews Cancer* 2:38-47.
- Hepple, R. T. 2000. Skeletal muscle: microcirculatory adaptation to metabolic demand. *Medicine and Science in Sports and Exercise* 32:117-123.
- Hochachka, P. W., Stanley, C., Merkt, J., & Sumar-Kalinowski, J. 1983. Metabolic meaning of elevated levels of oxidative enzymes in high altitude adapted animals: an interpretive hypothesis. *Respir.Physiol* 52:303-313.
- Hochachka, P. W. 1986. Balancing Conflicting Metabolic Demands of Exercise and Diving. *Federation Proceedings* 45:2948-2952.

- Hochachka, P. W. 1998. Mechanism and evolution of hypoxia-tolerance in humans. *J Exp.Biol* 201:1243-1254.
- Hodge, K., Powers, S. K., Coombes, J., Fletcher, L., Demirel, H. A., Dodd, S. L., & Martin, D. 1997. Bioenergetic characteristics of the costal and crural diaphragm in mammals. *Respiration Physiology* 109:149-154.
- Hoppeler, H., Lindstedt, S. L., Claassen, H., Taylor, C. R., Mathieu, O., & Weibel, E. R. 1984. Scaling mitochondrial volume in heart to body mass. *Respir.Physiol* 55:131-137.
- Hoppeler, H., Howald, H., Conley, K., Lindstedt, S. L., Claassen, H., Vock, P., & Weibel, E. R. 1985. Endurance training in humans: aerobic capacity and structure of skeletal muscle. *J Appl.Physiol* 59:320-327.
- Hoppeler, H. & Desplanches, D. 1992. Muscle Structural Modifications in Hypoxia. *International Journal of Sports Medicine* 13:S166-S168.
- Hoppeler, H. & Vogt, M. 2001. Muscle tissue adaptations to hypoxia. *Journal of Experimental Biology* 204:3133-3139.
- Howald, H., Pette, D., Simoneau, J. A., Uber, A., Hoppeler, H., & Cerretelli, P. 1990. Effects of Chronic Hypoxia on Muscle Enzyme-Activities. *International Journal of Sports Medicine* 11:S10-S14.
- Ishihara, A., Itoh, K., Oishi, Y., Itoh, M., Hirofuji, C., & Hayashi, H. 1995. Effects of Hypobaric Hypoxia on Histochemical Fiber-Type Composition and Myosin Heavy-Chain Isoform Component in the Rat Soleus Muscle. *Pflugers Archiv-European Journal of Physiology* 429:601-606.
- Itoh, K., Moritani, T., Ishida, K., Hirofuji, C., Taguchi, S., & Itoh, M. 1990. Hypoxia-induced fibre type transformation in rat hindlimb muscles. Histochemical and electromechanical changes. *Eur.J Appl.Physiol Occup.Physiol* 60:331-336.
- Jalil, J., Braun, S., Chamorro, G., Casanegra, P., Saldias, F., Beroiza, T., Foradori, A., Rodriguez, R., & Morales, M. 1994. [Cardiovascular response to exercise at high altitude in workers chronically exposed to intermittent hypobaric hypoxia]. *Rev.Med.Chil* 122:1120-1125.
- Jammes, Y., Zattara-Hartmann, M. C., & Badier, M. 1997. Functional consequences of acute and chronic hypoxia on respiratory and skeletal muscles in mammals. *Comp Biochem.Physiol A Physiol* 118:15-22.
- Jiang, B. H., Rue, E., Wang, G. L., Roe, R., & Semenza, G. L. 1996. Dimerization, DNA binding, and transactivation properties of hypoxia-inducible factor 1. *Journal of Biological Chemistry* 271:17771-17778.
- Kalaria, R. N., Spoor, L., Laude, E. A., Emery, C. J., Thwaites-Bee, D., Fairlie, J., Oakley, A. E., Barer, D. H., & Barer, G. R. 2004. Hypoxia of sleep apnoea: cardiopulmonary and cerebral changes after intermittent hypoxia in rats. *Respiratory Physiology & Neurobiology* 140:53-62.
- Kanatous, S. B., DiMichele, L. V., Cowan, D. F., & Davis, R. W. 1999. High aerobic capacities in the skeletal muscles of pinnipeds: adaptations to diving hypoxia. *Journal of Applied Physiology* 86:1247-1256.
- Kanatous, S. B. & Garry, D. J. 2006. Gene deletional strategies reveal novel physiological roles for myoglobin in striated muscle. *Respiratory Physiology & Neurobiology* 151:151-158.

- Kayser, B., Hoppeler, H., Claassen, H., & Cerretelli, P. 1991. Muscle structure and performance capacity of Himalayan Sherpas. *J Appl.Physiol* 70:1938-1942.
- Kayser, B., Hoppeler, H., Desplanches, D., Marconi, C., Broers, B., & Cerretelli, P. 1996. Muscle ultrastructure and biochemistry of lowland Tibetans. *J Appl.Physiol* 81:419-425.
- Kayar, S. R. & Banchero, N. 1985. Myocardial Capillarity in Acclimation to Hypoxia. *Pflugers Archiv-European Journal of Physiology* 404:319-325.
- Kellogg, R. H. 1978. "La Pression barometrique": Paul Bert's hypoxia theory and its critics. *Respir.Physiol* 34:1-28.
- Kennedy, S. L., Stanley, W. C., Panchal, A. R., & Mazzeo, R. S. 2001. Alterations in enzymes involved in fat metabolism after acute and chronic altitude exposure. *Journal of Applied Physiology* 90:17-22.
- Kotliarova, L.A., Ehrenbourg, I.V., Kondrykin-skaya, I.I., Gorbatchenkov, A.A. 1993. Interval hypoxic therapy in complex treatment of rheumatoid arthritis. *Hyp. Med. J* 1: 18.
- Kreutzer, U. & Jue, T. 2006. Investigation of bioactive NO-scavenging role of myoglobin in myocardium. *Pflugers Archiv-European Journal of Physiology* 452:36-42.
- Lahiri, S., Roy, A., Baby, S. M., Hoshi, T., Semenza, G. L., & Prabhakar, N. R. 2006. Oxygen sensing in the body. *Progress in Biophysics & Molecular Biology* 91:249-286.
- Lawler, J. M., Powers, S. K., Vandijk, H., Visser, T., Kordus, M. J., & Ji, L. L. 1994. Metabolic and Antioxidant Enzyme-Activities in the Diaphragm - Effects of Acute Exercise. *Respiration Physiology* 96:139-149.
- Lee-de Groot, M. B. E., des Tombe, A. L., & van der Laarse, W. J. 1998. Calibrated histochemistry of myoglobin concentration in cardiomyocytes. *Journal of Histochemistry & Cytochemistry* 46:1077-1084.
- Leon-Velarde, F., Sanchez, J., Bigard, A. X., Brunet, A., Lesty, C., & Monge, C. 1993. High-Altitude Tissue Adaptation in Andean Coots - Capillarity, Fiber Area, Fiber Type and Enzymatic-Activities of Skeletal-Muscle. *Journal of Comparative Physiology B-Biochemical Systemic and Environmental Physiology* 163:52-58.
- Levine, S., Gregory, C., Nguyen, T., Shrager, J., Kaiser, L., Rubinstein, N., & Dudley, G. 2002. Bioenergetic adaptation of individual human diaphragmatic myofibers to severe COPD. *Journal of Applied Physiology* 92:1205-1213.
- Levy, A. P., Levy N. S., Wegner S., & Goldberg M. A. 1995. Transcriptional regulation of the rat vascular endothelial growth factor gene by hypoxia. *J.Biol.Chem* 270: 13333-13340.
- Lewis, A. M., Mathieu-Costello, O., McMillan, P. J., & Gilbert, R. D. 1999. Effects of long-term, high-altitude hypoxia on the capillarity of the ovine fetal heart. (vol 277, pg H756, 1999). *American Journal of Physiology-Heart and Circulatory Physiology* 277:U28.
- Luedeke, J. D., Mccall, R. D., Dillaman, R. M., & Kinsey, S. T. 2004. Properties of slow- and fast-twitch skeletal muscle from mice with an inherited capacity for hypoxic exercise. *Comparative Biochemistry and Physiology A-Molecular & Integrative Physiology* 138:373-382.

- Mammen, P. P., White, J., McGrath, A. J., Kanatous, S. B., Horton, J. W., & Garry, D. J. 2003. Cardioprotective roles of myoglobin and cytoglobin in the ischemic heart. *Circulation* 108:291.
- Martcorena, E.A. 1998. Bases moleculares hipóxicas en rehabilitación cardíaca coronaria con altura natural y simulada. *Rev. Peruana de Cardiolog* 24: 2: 177-186.
- Martcorena, E. A., Martcorena, J. M., Gutierrez, I., Rodriguez, V., Fernandez-Davila, L., Oyola, L., Oré, R., Contreras, A., Valdivia, L., Robles, J., & Florentini, E. 2001. Factor relajante del endotelio (NO) en rehabilitación coronaria con cámara hipobárica. *Rev. Peruana de Cardiolog* 27: 2: 148-9.
- Mashkovskii, V. G. 1975. [Certain hemodynamic indicators during rest and after intensive physical exercise at high altitude]. *Kardiologiia* 15:61-67.
- Masuda, K., Choi, J. Y., Shimojo, H., & Katsuta, S. 1999. Maintenance of myoglobin concentration in human skeletal muscle after heavy resistance training. *European Journal of Applied Physiology* 79:347-352.
- Masuda, K., Okazaki, K., Kuno, S., Asano, K., Shimojo, H., & Katsuta, S. 2001. Endurance training under 2500-m hypoxia does not increase myoglobin content in human skeletal muscle. *European Journal of Applied Physiology* 85:486-490.
- Mathieu-Costello, O. 2001. Muscle adaptation to altitude: Tissue capillarity and capacity for aerobic metabolism. *High Altitude Medicine & Biology* 2:413-425.
- McGuire, M., MacDermott, M., & Bradford, A. 2003. Effects of chronic intermittent asphyxia on rat diaphragm and limb muscle contractility. *Chest* 123:875-881.
- 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. *Medicine and Science in Sports and Exercise* 29:238-243.
- Messonnier, L., Freund, H., Feasson, L., Prieur, F., Castells, J., Denis, C., Linossier, M. T., Geysant, A., & Lacour, J. R. 2001. Blood lactate exchange and removal abilities after relative high-intensity exercise: effects of training in normoxia and hypoxia. *European Journal of Applied Physiology* 84:403-412.
- Milano, G., Corno, A. F., Lippa, S., von Segesser, L. K., & Samaja, M. 2002. Chronic and intermittent hypoxia induce different degrees of myocardial tolerance to hypoxia-induced dysfunction. *Experimental Biology and Medicine* 227:389-397.
- Milledge, JS. 2003. Altitude Deterioration. En "Health and Height" C.Leal, A. Ricart G. Viscor (Eds). Publicaciones de la Universitat de Barcelona. 173-180.
- Millhorn, D. E., R. Raymond, L. Conforti, W. Zhu, D. Beitner-Johnson, T. Filisko, M. B. Genter, S. Kobayashi, & M. Peng. 1997. Regulation of gene expression for tyrosine hydroxylase in oxygen sensitive cells by hypoxia. *Kidney Int* 51: 527-535.
- Millikan GA 1939. Muscle haemoglobin. *Physiol Rev* 19:503-523.
- Mittal, R. K., Rochester, D. F., & McCallum, R. W. 1988. Electrical and mechanical activity in the human lower esophageal sphincter during diaphragmatic contraction. *J Clin.Invest* 81:1182-1189.
- Moore, R. L. & Gollnick, P. D. 1982. Response of Ventilatory Muscles of the Rat to Endurance Training. *Pflugers Archiv-European Journal of Physiology* 392:268-271.

- Moore, M., Allison, D., & Rosen, C. L. 2006. A review of pediatric nonrespiratory sleep disorders. *Chest* 130:1252-1262.
- Morel, O. E., Aubert, R., Richalet, J. P., & Chapelot, D. 2005. Simulated high altitude selectively decreases protein intake and lean mass gain in rats. *Physiol Behav* 86:145-153.
- Murakami, T., Shimomura, Y., Fujitsuka, N., Nakai, N., Sugiyama, S., Ozawa, T., Sokabe, M., Horai, S., Tokuyama, K., & Suzuki, M. 1994. Enzymatic and Genetic Adaptation of Soleus Muscle Mitochondria to Physical-Training in Rats. *American Journal of Physiology* 267:E388-E395.
- Nachlas, M. M., Tsou, K. C., de, S E., Cheng, C. S., & Seligman, A. M. 1957. Cytochemical demonstration of succinic dehydrogenase by the use of a new p-nitrophenyl substituted ditetrazole. *J Histochem Cytochem* 5:420-436.
- Neubauer, J. A. 2001. Physiological and genomic consequences of intermittent hypoxia - Invited review: Physiological and pathophysiological responses to intermittent hypoxia. *Journal of Applied Physiology* 90:1593-1599.
- Ogura, Y., Naito, H., Aoki, J., Uchimarui, J., Sugiura, T., & Katamoto, S. 2005. Sprint-interval training-induced alterations of myosin heavy chain isoforms and enzyme activities in rat diaphragm: Effect of normobaric hypoxia. *Japanese Journal of Physiology* 55:309-316.
- Ohtsuka, T. & Gilbert, R. D. 1995. Cardiac Enzyme-Activities in Fetal and Adult Pregnant and Nonpregnant Sheep Exposed to High-Altitude Hypoxemia. *Journal of Applied Physiology* 79:1286-1289.
- Ordway, G. A. & Garry, D. J. 2004. Myoglobin: an essential hemoprotein in striated muscle. *Journal of Experimental Biology* 207:3441-3446.
- Orozco-Levi, M., Gea, J., Lloreta, J. L., Felez, M., Minguella, J., Serrano, S., & Broquetas, J. M. 1999. Subcellular adaptation of the human diaphragm in chronic obstructive pulmonary disease. *European Respiratory Journal* 13:371-378.
- Ostadal, B., Urbanova, D., Ressler, J., Prochazka, J., Pelouch, V., & Widimsky, J. 1981. Changes of the Right and Left-Ventricles in Rats Exposed to Intermittent High-Altitude Hypoxia. *Cor et Vasa* 23:111-120.
- Padykula, H. A. & Herman, E. 1955a. The Specificity of the Histochemical Method for Adenosine Triphosphatase. *Journal of Histochemistry & Cytochemistry* 3:170-195.
- Padykula, H. A. & Herman, E. 1955b. Factors Affecting the Activity of Adenosine Triphosphatase and Other Phosphatases As Measured by Histochemical Techniques. *Journal of Histochemistry & Cytochemistry* 3:161-169.
- Pages, T. & Planas, J. 1983. Muscle Myoglobin and Flying Habits in Birds. *Comparative Biochemistry and Physiology A-Physiology* 74:289-294.
- Pastoris, O., Foppa, P., Catapano, M., & Dossena, M. 1995. Effects of hypoxia on enzyme activities in skeletal muscle of rats of different ages. An attempt at pharmacological treatment. *Pharmacological Research* 32:375-381.
- Peacock, A. J. 1998. ABC of oxygen - Oxygen at high altitude. *British Medical Journal* 317:1063-1066.

- Perhonen, M., Takala, T. E. S., & Kovanen, V. 1996. Effects of prolonged exposure to and physical training in hypobaric conditions on skeletal muscle morphology and metabolic enzymes in rats. *Pflugers Archiv-European Journal of Physiology* 432:50-58.
- Peter, J. B., Barnard, R. J., Edgerton, V. R., Gillespie, C. A., & Stempel, K. E. 1972. Metabolic profiles of three fiber types of skeletal muscle in guinea pigs and rabbits. *Biochemistry* 11:2627-2633.
- Pette, D. & Staron, R. S. 1990. Cellular and molecular diversities of mammalian skeletal muscle fibers. *Rev.Physiol Biochem.Pharmacol* 116:1-76.
- Pietschmann, M. & Bartels, H. 1985. Cellular Hyperplasia and Hypertrophy, Capillary Proliferation and Myoglobin Concentration in the Heart of Newborn and Adult-Rats at High-Altitude. *Respiration Physiology* 59:347-360.
- Pissarek, M., Bigard, X., Mateo, P., Guezennec, C. Y., & Hoerter, J. A. 1997. Adaptation of cardiac myosin and creatine kinase to chronic hypoxia: Role of anorexia and hypertension. *American Journal of Physiology-Heart and Circulatory Physiology* 41:H1690-H1695.
- Polla, B., D'Antona, G., Bottinelli, R., & Reggiani, C. 2004. Respiratory muscle fibres: specialisation and plasticity. *Thorax* 59:808-817.
- Powers, S. K., Lawler, J., Criswell, D., Silverman, H., Forster, H. V., Grinton, S., & Harkins, D. 1990. Regional Metabolic Differences in the Rat Diaphragm. *Journal of Applied Physiology* 69:648-650.
- Powers, S. K. & Criswell, D. 1996. Adaptive strategies of respiratory muscles in response to endurance exercise. *Medicine and Science in Sports and Exercise* 28:1115-1122.
- Puente-Maestu, L., Tena, T., Trascasa, C., Perez-Parra, J., Godoy, R., Garcia, M. J., & Stringer, W. W. 2003. Training improves muscle oxidative capacity and oxygenation recovery kinetics in patients with chronic obstructive pulmonary disease. *European Journal of Applied Physiology* 88:580-587.
- Prabhakar, N. R. 2000. Oxygen sensing by the carotid body chemoreceptors. *Journal of Applied Physiology* 88:2287-2295.
- Prabhakar, N. R. 2001. Physiological and genomic consequences of intermittent hypoxia - Invited review: Oxygen sensing during intermittent hypoxia: cellular and molecular mechanisms. *Journal of Applied Physiology* 90:1986-1994.
- Prabhakar, N. R., Fields, R. D., Baker, T., & Fletcher, E. C. 2001. Intermittent hypoxia: cell to system. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 281:L524-L528.
- Prabhakar, N. R. 2002. Sleep apneas: an oxidative stress? *Am J Respir.Crit Care Med.* 165:859-860.
- Prabhakar, N. R. 2006. O₂ sensing at the mammalian carotid body: why multiple O₂ sensors and multiple transmitters? *Experimental Physiology* 91:17-23.
- Raff, H., Bruder, E. D., & Jankowski, B. M. 1999. The effect of hypoxia on plasma leptin and insulin in newborn and juvenile rats. *Endocrine* 11:37-39.
- Reed, J. Z., Butler, P. J., & Fedak, M. A. 1994. The Metabolic Characteristics of the Locomotory Muscles of Grey Seals (*Halichoerus-Grypus*), Harbor Seals (*Phoca-*

- Vitulina) and Antarctic fur Seals (*Arctocephalus-Gazella*). *Journal of Experimental Biology* 194:33-46.
- Reid, M. B., Parsons, D. B., Giddings, C. J., Gonyea, W. J., & Johnson, R. L. 1992. Capillaries Measured in Canine Diaphragm by 2 Methods. *Anatomical Record* 234:49-54.
- Reis, D. J. & Wooten, G. F. 1970. Relationship of Blood Flow to Myoglobin, Capillary Density, and Twitch Characteristics in Red and White Skeletal Muscle in Cat. *Journal of Physiology-London* 210:121-&.
- Reynafarje, B. 1962. Myoglobin content and enzymatic activity of muscle and altitude adaptation. *J Appl.Physiol* 17:301-305.
- Reynafarje, B. & Morrisson, P. 1962. Myoglobin levels in some tissues from wild Peruvian rodents native to high altitude. *J Biol.Chem* 237:2861-2864.
- Reynafarje, B. 1963. Simplified method for the determination of myoglobin. *J Lab Clin.Med* 61:138-145.
- Reynafarje, B. & Velasquez, T. 1966. Metabolic and physiological aspects of exercise at high altitude. I. Kinetics of blood lactate, oxygen consumption and oxygen debt during exercise and recovery breathing air. *Fed.Proc* 25:1397-1399.
- Ricart, A., Casas, H., Casas, M., Pages, T., Palacios, L., Rama, R., Rodriguez, F. A., Viscor, G., & Ventura, J. L. 2000. Acclimatization near home? Early respiratory changes after short-term intermittent exposure to simulated altitude. *Wilderness & Environmental Medicine* 11:84-88.
- Richalet, J. P., Keromes, A., Carillion, A., Mehdioui, H., Larmignat, P., & Rathat, C. 1989. [Cardiac response to hypoxia and susceptibility to mountain sickness]. *Arch.Mal Coeur Vaiss* 82 Spec No 2:49-54.
- Richalet, J. P., Bittel, J., Herry, J. P., Savourey, G., Le Trong, J. L., Auvert, J. F., & Janin, C. 1992. Use of a hypobaric chamber for pre-acclimatization before climbing Mount Everest. *Int.J Sports Med* 13 Suppl 1:S216-S220.
- Richalet, J. P. 1997. Oxygen sensors in the organism: examples of regulation under altitude hypoxia in mammals. *Comp Biochem.Physiol A Physiol* 118:9-14.
- Richalet, J. P., Donoso, M. V., Jimenez, D., Antezana, A. M., Hudson, C., Cortes, G., Osorio, J., & Leon, A. 2002. Chilean miners commuting from sea level to 4500 m: a prospective study. *High Alt.Med.Biol* 3:159-166.
- Rodriguez, F. A., Casas, H., Casas, M., Pages, T., Rama, R., Ricart, A., Ventura, J. L., Ibanez, J., & Viscor, G. 1999. Intermittent hypobaric hypoxia stimulates erythropoiesis and improves aerobic capacity. *Medicine and Science in Sports and Exercise* 31:264-268.
- Rodriguez, F. A., Ventura, J. L., Casas, M., Casas, H., Pages, T., Rama, R., Ricart, A., Palacios, L., & Viscor, G. 2000. Erythropoietin acute reaction and haematological adaptations to short, intermittent hypobaric hypoxia. *European Journal of Applied Physiology* 82:170-177.
- Rose, M. S., Houston, C. S., Fulco, C. S., Coates, G., Sutton, J. R., & Cymerman, A. 1988. Operation Everest .2. Nutrition and Body-Composition. *Journal of Applied Physiology* 65:2545-2551.

- Rosenblatt, J. D., Kuzon, W. M., Plyley, M. J., Pynn, B. R., & Mckee, N. H. 1987. A Histochemical Method for the Simultaneous Demonstration of Capillaries and Fiber Type in Skeletal-Muscle. *Stain Technology* 62:85-92.
- Rossignol, F., Solares, M., Balanza, E., Coudert, J., & Clottes, E. 2003. Expression of lactate dehydrogenase A and B genes in different tissues of rats adapted to chronic hypobaric hypoxia. *Journal of Cellular Biochemistry* 89:67-79.
- Rumsey, W. L., Abbott, B., Bertelsen, D., Mallamaci, M., Hagan, K., Nelson, D., & Erecinska, M. 1999. Adaptation to hypoxia alters energy metabolism in rat heart. *American Journal of Physiology-Heart and Circulatory Physiology* 276:H71-H80.
- Saltin, B., Nygaard, E., & Rasmussen, B. 1980. Skeletal-Muscle Adaptation in Man Following Prolonged Exposure to High-Altitude. *Acta Physiologica Scandinavica* 109:A31.
- Sanchez, J., Sarue, A. M., Brunet, A., & Monod, H. 1991. Enzymatic Adaptations to Treadmill Training Under the Influence of Naftidrofuryl Acid in Diaphragm and Limb Muscles of Old Rats. *Archives Internationales de Physiologie de Biochimie et de Biophysique* 99:129-134.
- Sauleda, J., Garcia-Palmer, F., Wiesner, R. J., Tarraga, S., Harting, I., Tomas, P., Gomez, C., Saus, C., Palou, A., & Agusti, A. G. 1998. Cytochrome oxidase activity and mitochondrial gene expression in skeletal muscle of patients with chronic obstructive pulmonary disease. *Am J Respir. Crit Care Med* 157:1413-1417.
- Semenza, G. L., B. H. Jiang, S. W. Leung, R. Passantino, J. P. Concordet, P. Maire, & A. Giallongo. 1996. Hypoxia response elements in the aldolase A, enolase 1, and lactate dehydrogenase A gene promoters contain essential binding sites for hypoxia-inducible factor 1. *J. Biol. Chem* 271: 32529-32537.
- Semenza, G. L. 2000a. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *Journal of Applied Physiology* 88:1474-1480.
- Semenza, G. L. 2000b. HIF-1: Using two hands to flip the angiogenic switch. *Cancer and Metastasis Reviews* 19:59-65.
- Semenza, G. L. 2002. Signal transduction to hypoxia-inducible factor 1. *Biochemical Pharmacology* 64:993-998.
- Semenza, G. L. Transcriptional Regulation by Hypoxia-Inducible Factor 1. 2003. Molecular Mechanisms of Oxygen Homeostasis. *Trends in Cardiovascular Medicine* 6: 151-157.
- Sexton, W. L. & Poole, D. C. 1995. Costal Diaphragm Blood-Flow Heterogeneity at Rest and During Exercise. *Respiration Physiology* 101:171-182.
- Scheuermann, D. W. 1993. The Ultrastructure of Cardiac-Muscle in Health and Disease. *Micron* 24:47-73.
- Schiaffino, S. & Reggiani, C. 1994. Myosin isoforms in mammalian skeletal muscle. *J Appl. Physiol* 77:493-501.
- Schiaffino, S. & Reggiani, C. 1996. Molecular diversity of myofibrillar proteins: gene regulation and functional significance. *Physiol Rev* 76:371-423.

- Schmidt, M., Gerlach, F., Avivi, A., Laufs, T., Wystub, S., Simpson, J. C., Nevo, E., Saaler-Reinhardt, S., Reuss, S., Hankeln, T., & Burmester, T. 2004. Cytoglobin is a respiratory protein in connective tissue and neurons, which is up-regulated by hypoxia. *J Biol.Chem* 279:8063-8069.
- Schumacker, P. T. 2002. Hypoxia, anoxia, and O-2 sensing: the search continues. *American Journal of Physiology-Lung Cellular and Molecular Physiology* 283:L918-L921.
- Sheafor, B. A. 2003. Metabolic enzyme activities across an altitudinal gradient: an examination of pikas (genus Ochotona). *Journal of Experimental Biology* 206:1241-1249.
- Shima, D. T., Adamis, A. P., Ferrara, N., Yeo, K. T., Yeo, T. K., Allende, R., Folkman, J., & D'Amore, P. A. 1995. Hypoxic induction of endothelial cell growth factors in retinal cells: identification and characterization of vascular endothelial growth factor (VEGF) as the mitogen. *Mol.Med* 1:182-193.
- Sicard, B., Jouve, E., & Blin, O. 2001. Risk propensity assessment in military special operations. *Mil.Med* 166:871-874.
- Sicard, B., Taillemite, J. P., Jouve, E., & Blin, O. 2003. Risk propensity in commercial and military pilots. *Aviat.Space Environ.Med* 74:879-881.
- Sieck, G. C., Sacks, R. D., & Blanco, C. E. 1987. Absence of Regional Differences in the Size and Oxidative Capacity of Diaphragm Muscle-Fibers. *Journal of Applied Physiology* 63:1076-1082.
- Sieck, G. C. 1988. Diaphragm Muscle - Structural and Functional-Organization. *Clinics in Chest Medicine* 9:195-210.
- Sieck, G. C. 2004. Oxygen sensing in health and disease. *Journal of Applied Physiology* 96:1-2.
- Singh, S. B. & Selvamurthy, W. 1993. Effect of Intermittent Chronic Exposure to Hypoxia on Feeding-Behavior of Rats. *International Journal of Biometeorology* 37:200-202.
- Siren, A. L. & Ehrenreich, H. 2001. Erythropoietin--a novel concept for neuroprotection. *Eur.Arch.Psychiatry Clin.Neurosci* 251:179-184.
- Siu, P. M., Donley, D. A., Bryner, R. W., & Alway, S. E. 2003. Citrate synthase expression and enzyme activity after endurance training in cardiac and skeletal muscles. *Journal of Applied Physiology* 94:555-560.
- Snyder, G. K., Wilcox, E. E., & Burnham, E. W. 1985. Effects of Hypoxia on Muscle Capillarity in Rats. *Respiration Physiology* 62:135-140.
- Smith, D., Green, H., Thomson, J., & Sharratt, M. 1989. Capillary and size interrelationships in developing rat diaphragm, EDL, and soleus muscle fiber types. *Am J Physiol* 256:C50-C58.
- Sokal RR & Rohlf FJ 1981, *Biometry: the Principles and practice of Statistics in Biological Research* New York: WH Freeman.
- Sokolov, A.A., Dudkina, Yu.V., Dudko, V.A., Kulemzin, A.V., Tarasov, M.G. 1994. The effect of a seance of dosed hypercapnic hypoxia on parameters of the cardiorespiratory system in patients with ischemic heart disease. *Hyp. Med. J* 2: 3: 19-21.

- Sokolov, E.I., Mushinskaya, K.V., Davydov, A.L., Starkova, N.T., Ehrenburg, I.V., Tkatchouk, E.N. 1999. Effects of the interval hypoxic training on lipid peroxidation in non-insulin-dependent diabetes mellitus. *Hyp.Med.J* 3: 4: 37-40.
- Srere P.A. 1969, Citrate synthase, In "Methods in Enzymology Citric. Acid Cycle", Volume 13 by N.P. Kaplan and N.P. Colowick (Editors), pp. 3-5.
- Sugiura, T., Morita, S., Morimoto, A., & Murakami, N. 1992. Regional Differences in Myosin Heavy-Chain Isoforms and Enzyme-Activities of the Rat Diaphragm. *Journal of Applied Physiology* 73:506-509.
- Sun, Y. J., Jin, K. L., Peel, A., Mao, X. O., Xie, L., & Greenberg, D. A. 2003. Neuroglobin protects the brain from experimental stroke in vivo. *Proceedings of the National Academy of Sciences of the United States of America* 100:3497-3500.
- Suzuki, J. 2002. Microvascular remodelling after endurance training with Co²⁺ treatment in the rat diaphragm and hind-leg muscles. *Japanese Journal of Physiology* 52:409-419.
- Tateishi-Yuyama, E., Matsubara, H., Murohara, T., Ikeda, U., Shintani, S., Masaki, H., Amano, K., Kishimoto, Y., Yoshimoto, K., Akashi, H., Shimada, K., Iwasaka, T., & Imaizumi, T. 2002. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet* 360:427-435.
- Takahashi, E., Sato, K., Endoh, H., Xu, Z. L., & Doi, K. 1998. Direct observation of radial intracellular Po₂ gradients in a single cardiomyocyte of the rat. *American Journal of Physiology-Heart and Circulatory Physiology* 44:H225-H233.
- Tamaki, N. 1985. Effect of Growth on Muscle Capillarity and Fiber Type Composition in Rat Diaphragm. *European Journal of Applied Physiology and Occupational Physiology* 54:24-29.
- Tappan, D. V. & Reynafarje, B. 1957. Tissue pigment manifestations of adaptation to high altitudes. *Am J Physiol* 190:99-103.
- Taylor, C. R. & Weibel, E. R. 1981. Design of the mammalian respiratory system. I. Problem and strategy. *Respir.Physiol* 44:1-10.
- Terrados, N., Jansson, E., Sylven, C., & Kaijser, L. 1990. Is Hypoxia A Stimulus for Synthesis of Oxidative-Enzymes and Myoglobin. *Journal of Applied Physiology* 68:2369-2372.
- Thomas, T. & Marshall, J. M. 1997. The roles of adenosine in regulating the respiratory and cardiovascular systems in chronically hypoxic, adult rats. *J Physiol* 501 (Pt 2):439-447.
- Tkatchouk, E.N. 1993. Effectiveness of interval hypoxic training in surgery: prevention of postoperative uterine myoma complications. *Hyp. Med. J.* 1: 3: 17-21.
- Torrella, J. R., Fouces, V., Palomeque, J., & Viscor, G. 1998. Comparative skeletal muscle fibre morphometry among wild birds with different locomotor behaviour. *Journal of Anatomy* 192:211-222.
- Torrella, J. R., Whitmore, J. M., Casas, M., Fouces, V., & Viscor, G. 2000. Capillarity, fibre types and fibre morphometry in different sampling sites across and along the tibialis anterior muscle of the rat. *Cells Tissues Organs* 167:153-162.

- Tschop, M. & Morrison, K. M. 2001, Weight loss at high altitude Kluwer academic/plenum publ, New York.
- Unruh, A., Ressel, A., Mohamed, H. G., Johnson, R. S., Nadrowitz, R., Richter, E., Katschinski, D. M., & Wenger, R. H. 2003. The hypoxia-inducible factor-1 alpha is a negative factor for tumor therapy. *Oncogene* 22:3213-3220.
- Uribe, J. M., Stump, C. S., Tipton, C. M., & Fregosi, R. F. 1992. Influence of Exercise Training on the Oxidative Capacity of Rat Abdominal Muscles. *Respiration Physiology* 88:171-180.
- Valdivia, E. 1958. Total capillary bed in striated muscles of guinea pigs native to the Peruvian mountains. *Am J Physiol* 194:585-589.
- Valle, M. D., Garcia-Godos, F., Woolcott, O. O., Marticorena, J. M., Rodriguez, V., Gutierrez, I., Fernandez-Davila, L., Contreras, A., Valdivia, L., Robles, J., & Marticorena, E. A. 2006. Improvement of myocardial perfusion in coronary patients after intermittent hypobaric hypoxia. *Journal of Nuclear Cardiology* 13:69-74.
- Van Liere EJ & Stickney JC 1964, *Hypoxia* University of Chicago Press.
- Vergnes, H. 1971. Modifications in Activity of Enzymes in Extracts from Myocardia of Rats Living at High-Altitudes. *Cardiology* 56:222-&.
- Viscor, G., Casas, H., Casas, M., Palacios, L., Rama, R., & Pages, T. 2000. Blood rheology after intermittent hypobaric hypoxia pre-acclimation programs. *High Alt.Med.Biol* 1, 271.
- 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. *Journal of Applied Physiology* 91:173-182.
- Ward, M.P., Milledge, J.S., & West, J.B. 2000, 3rd Edition, *High altitude medicine and Physiology* Arnold publishers, New York. Chapter 8.
- Wenger, R. H. 2000. Mammalian oxygen sensing, signalling and gene regulation. *Journal of Experimental Biology* 203:1253-1263.
- Wenger, R. H. 2006. Mitochondria: Oxygen sinks rather than sensors? *Medical Hypotheses* 66:380-383.
- West, J. B. 1993. Acclimatization and tolerance to extreme altitude. *J Wilderness Med* 4:17-26.
- West, J. B. 1998, *High life: a history of high-altitude physiology and medicine*. The American physiological society. Oxford University Press.
- West, J. B. 2002. Highest permanent human habitation. *High Alt.Med.Biol.* 3:401-407.
- West, J. B. 2004. The physiologic basis of high-altitude diseases. *Annals of Internal Medicine* 141:789-800.
- Whitelaw, W. A. 1987. Shape and size of the human diaphragm in vivo. *J Appl.Physiol* 62:180-186.
- Wittenberg, B. A. & Wittenberg, J. B. 1989. Transport of Oxygen in Muscle. *Annual Review of Physiology* 51:857-878.
- Wittenberg, J. B. & Wittenberg, B. A. 2003. Myoglobin function reassessed. *Journal of Experimental Biology* 206:2011-2020.

- Xie, Z. L., Gao, M., & Koyama, T. 1997. Effects of transient coronary occlusion on the capillary network in the left ventricle of rat. *Japanese Journal of Physiology* 47:537-543.
- Yamashita, H., Nakanishi, K., Tajima, F., Sato, Y., Kizaki, T., Ohishi, S., & Ohno, H. 1994. Chronic Exposure to Simulated Altitude Does Not Increase Angiogenic Activity in Skeletal-Muscle of Rats. *Tohoku Journal of Experimental Medicine* 172:375-379.
- Yuan, G. X., Nanduri, J., Bhasker, C. R., Semenza, G. L., & Prabhakar, N. R. 2005. Ca²⁺/calmodulin kinase-dependent activation of hypoxia inducible factor 1 transcriptional activity in cells subjected to intermittent hypoxia. *Journal of Biological Chemistry* 280:4321-4328.
- Zhu, Y. H., Sun, Y. J., Jin, K. L., & Greenberg, D. A. 2002. Hemin induces neuroglobin expression in neural cells. *Blood* 100:2494-2498.
- Zhuang, J. & Zhou, Z. 1999. Protective effects of intermittent hypoxic adaptation on myocardium and its mechanisms. *Biol. Signals Recept* 8:316-322.
- Zobundzija, M., Novak, R., Kozaric, Z., Mihelic, D., & Brkic, A. 1998. The morphohistochemical analysis of the pars costalis and pars lumbalis diaphragmae in lambs. *Veterinarni Medicina* 43:357-360.
- Zúñiga, J.M., Tur Marí, J.A., Milocco, S.N., & Piñeiro, R. 2001. Ciencia y tecnología en protección y experimentación animal. Ed. M^c Graw-Hill. Interamericana.