Acta Andina (1999-2000) 8: 39-45

# IMPACT AND MID-TERM ASSESSMENT OF CORONARY PATIENTS REHABILITATED WITH INTERMITTENT SIMULATED HYPOXIA TECHNIQUE[1]

**Emilio A. Marticorena; José M. Marticorena; Luz Oyola Bardalez; Víctor Rodríguez; Félix García Godos; David Alfaro; Luis Fernández Dávila; Ricardo Coloma; Abel Contreras Gonzalez; Isabel Gutiérrez; Camilo Zamora; Félix Villavicencio.**

**Instituto Nacional de Biología Andina, Facultad de Medicina, Universidad Nacional Mayor de San Marcos; Fuerza Aérea Peruana, "Hospital Las Palmas y Hospital Central", Lima-Perú.**

## RESUMEN

El objetivo principal de la presente investigación fue evaluar el impacto de la técnica de altura simulada con cámara hipobárica en rehabilitación de pacientes con revascularización coronaria con y sin infarto de miocardio.

Las siguientes variables, pre y post rehabilitación luego de programa cuatro meses después, mostraron recuperación hasta el final del tiempo de observación (4 meses) siguiendo el protocolo previamente establecido.

Dado que no hubo participación de actividad física/ aeróbica programada los resultados se consideran vinculados preferentemente al efecto de la hipoxia y consecuencia de cambios centrales más que periféricos.

Palabras Clave: Rehabilitación Coronaria, Hipoxia, Arritmia, Isquemia, Potenciales Tardíos, Perfusión, Bioquímica.

## SUMMARY

Main objetive of the present investigation were evaluate the impact of the simulated hypoxia technique – hypobaric chamber – to rehabilitate coronary bypassed with of without myocardial infarction.

The following variable, pre and post rehabilitation four months program were explored: myocardial ischemia, arrythmia, late potencials, myocardium perfussion and molecular biochemistry. The last two were observed in follow up of four months. Results, shows general improvement. The follow up items, remained improved until protocol finish. Exercise was not utilized. Findings are consider principally related to hypoxia. Mainly due to central rather than pheriphery recoveries.

Keywords: Coronary Rehabilitation, Hypoxia, Arrythmia, Ischemia, Late Potencials, Perfussion, Biochemistry.

## INTRODUCTION

Previous observations utilizing high altitude hypoxia (HAH) to rehabilitate coronary bypassed patients with or without myocardial infarction, shows a quickly recovery (Marticorena, 1984-85; Marticorena and Marticorena, 1990; Marticorena et al 1993). Because in this procedure, patient does exercise while are mountaineering, an hypobaric chamber hypoxia (HCHH) was utilized to test such type of environment. Results showed similar and consistent improvement on pheripheral central and metabolic parameters (Marticorena et al 1993; Marticorena et al 1994; Marticorena et al 1995; Marticorena et al 1995). There after, we did search for additional variables focusing on: 1) Effect of hypobaric hypoxia (HH) on myocardium ischemia and conduction system, 2) Four months follow up of: a) myocardium perfussion and b) molecular biochemistry.

## MATERIAL AND METHODS

### HYPOXIA HYPOBARIC CHAMBER TECHNIQUE

Simulated hypoxia technique utilizing hypobaric chamber, follows procedures based in a natural high altitude technique, developed by (Marticorena, 1984-85; Marticorena and Marticorena, 1990; Marticorena et al 1993; Marticorena 1993). It consist in intermittent and progressive hypoxia exposure begining at sea level and finishing at 5000 m. Session, were scheduled in a weekly basses, for four hours each time, during four consecutive months (Marticorena et al 1993; Marticorena et al 1994; Marticorena et al 1995; Marticorena et al 1995).

[1] Presented at the Second World Congress on High Altitude Medicine and Physiology. Cuzco, Perú, September 24-27, 1996.

Correspondece to: Emilio A. Marticorena, M.D. Papini 161, Lima 41, Perú

## SERIAL OF PATIENTS. PROCEDURES

### Series A
### Patients

Five patients, all men, age range 44 to 67 years, mean 57. All hypertensive; three with old myocardial infarct; one with angina. Elapsed surgery time, between 10 years and 2 months and 1 year and 3 months, mean 3 and 5 m. Number of coronary grafts between one and four.

### Procedures
### Myocardial Ischemia and Arrythmias

Centra Multifunction Cardiology Workstation Marquette Electronics, USA, Centra Holter System – Software Enhancements – version 002 D, were utilized. Twenty four hours regular procedure were used to investigate myocardial ischemia and arrythmias (Deedwania 1992). This includes four hours of patient under simulated hypoxia.

### Myocardial Perfussion

Myocardial perfussion were obtained on rest and exercise by standar plannar procedure utilizing Elscint 415 – W Unit. MIBI – TC 99 m (metil butil isonitrilo – tecnecio m) in uniform doses were used. The observation were not quantified. Three controls were taking. First, previous HCHH program, second after programs finish, and third four months later.

### Molecular Biochemistry

Hewlett Packard Spectrophotometer 89532A UV – Visible Unit, USA were utilized to evaluate molecular biochemistry, according Adams method (Adams 1963). Controls did follow myocardial perfusion schedule.

### Serie B
### Patients

Eight patients, seven man, one famale. Five hypertensive. Four with old myocardial infarct, two with arrythmia, one with angina. Elapsed surgery time, between 12 years and 5 months, mean 3 and 5 m. Number of coronary grafts between four and two.

### Procedure

### Late potencials

Multifunction Cardiology Workstation – Marquette Electronics, USA. Centra 306 DB Software were utilized to register late potencials signals.

## STATISTIC ANALYSIS

The paired t test was applied to compare the variables between pre and post, 2 and 4 months after simulated hypoxia program.

## RESULTS

### Serie A

### Myocardial Ischemia

No myocardial ischemia appeared in any patients at the time were exposed up to 5000m, highest limit for the protocol. A tendency to diminish ST depression were observed in one, became isoelectric in other, and remained normal in other three. Table 1.

TABLE 1. Coronary Rehabilitation with high altitude simulated Hypoxia

| 24 HOLTER MONITORING: S-T CHANGES | | | |
|---|---|---|---|
| SUBJECT No. (Age) | INITIAL SL. CONTROL (18 h) ST ↓ mm | HYPOB. CHAMBER (4h) 5000m ST ↓ mm | SL FINAL CONTROL (2h) ST ↓ mm |
| 1 (44) | — | — | — |
| 2 (52) | — | — | — |
| 3 (60) | — | — | — |
| 4 (62) | 12-0.4 | 0.6 | 0.6-0.5 |
| 5 (67) | 0.2 | — | — |

ST = S-T segment changes. SL = sea level.

No single patient became abnormal on S-T. On contrary, under hypoxia S-T depression diminish in patient 4 and became isoelectric in patient 5.

### Arrythmias

Consistent diminution of supraventricular and ventricular extrasistolia during hypoxia (H) were appreciated in all patients. Table 2.

TABLE 2. Coronary Rehabilitation with high altitude simulated Hypoxia

| 24 HOLTER MONITORING: P. VENT. CT | | | | | | |
|---|---|---|---|---|---|---|
| SUBJECT No. (Age) | INITIAL SL. CONTROL (18 h) | | HYPOB. CHAMBER (4h) 5000m | | SL FINAL CONTROL (2h) | |
| | SUP.CT. | P.VENT. CT. | SUP.CT. | P.VENT.CT. | SUP.CT. | P.VENT. CT. |
| 1 (44) | 1 - 0 | 2 - 0 | — | 1 - 0 | — | — |
| 2 (52) | 1 - 0 | 7 - 0 | — | 1 - 0 | — | — |
| 3 (60) | 3 - 0 | 266 - 2 | 1 - 0 | 1 - 0 | 5 - 0 | 16 - 0 |
| 4 (62) | 2 - 0 | 3 - 0 | 1 - 0 | 1 - 0 | — | — |
| 5 (67) | 5 - 0 | 18 - 1 | — | 2 - 0 | — | — |

SL = sea level. SUP.CT = supraventricular contraction. P.VENT.CT = premature ventricular contraction.

During hypoxia all patients diminish both, supraventricular and ventricle contractions.

### Myocardial Perfussion

In all patients showing myocardial ischemia, increased myocardial perfussion were found after four months HCHH program. This myocardium improvement did remain stable in the following four months control. Table 3.

TABLE 3. Coronary Rehabilitation with high altitude simulated Hypoxia

| MYOCARDIAL PERFUSSION - FOLLOW UP OBSERVATIONS | | | | |
|---|---|---|---|---|
| SUBJECT No. (Age) | COMPROMISE | BASELINE | END OF 4 MOS. PROG. | 4 MOS. AFTER END OF PROG. |
| 1 (44) | Inf. Post. | Isch. + | Isch.- | Isch.- |
| 2 (52) | Ant. Apic. | Isch. + | Isch.- | Isch.- |
| 3 (60) | Ant. Sept.<br>Diaphr.<br>Diaphr. | Isch. ++<br>Isch. +<br>Nec. + | Isch.+<br>Isch.-<br>Nec.+ | Isch.+<br>Isch.+<br>Nec.+ |
| 4 (62) | Inf. Apic.<br>Inf. Apic. | Isch. +<br>Nec. + | Isch.-<br>Nec.+ | Isch.-<br>Nec.+ |
| 5 (67) | Post. Lat.<br>Post. Lat. | Isch.-<br>Nec. ++ | Isch.-<br>Nec.++ | Isch.-<br>Nec.++ |

Isch = ischemia. nec. necrosis

All Patients who had myocardial ischemia improved. All benefits remained improved up to last control.

## Molecular Biochemistry

Improvement of metabolic performance at the end of four months regular program were found. Those values remained improved statisticaly significant up to end of the protocol, four months later. Table 4 and 5.

TABLE 4. Coronary Rehabilitation with high altitude simulated Hypoxia

| MOLECULAR BIOCHEMISTRY - FOLLOW UP OBSERVATION | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2- 3 DPG (4.5 - 5.5 u mol/ml) | | | | ATP (38 - 62 u mol/dl) | | | |
| B | F | 2M | 4M | B | F | 2M | 4M |
| 5 | 21 | 19 | 16 | 36 | 67 | 56 | 52 |
| p <0.001 <0.001 <0.001 | | | | <0.01 <0.01 <0.01 | | | |

2 - 3 DGP = 2 - 3 Diphosphogliceric acid. ATP = adenosine 5´ triphosphate. B = basal. F = final. 2M = two months control. 4M = four months control.

Both variables became early stimulated by hypoxia and remained similar until the last control.

TABLE 5. Coronary Rehabilitation with high altitude simulated Hypoxia

| MOLECULAR BIOCHEMISTRY - FOLLOW UP OBSERVATION | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ICDH 40-360 (U/ml) | | | | HBDH 56-126 (U/L) | | | LDH 125-236 (U/L 25°C) | | | | |
| B | F | 2M | 4M | B | F | 4M | B | F | 2M | 4M | |
| 93 | 239 | 171 | 168 | 56 | 93 | 70 | 65 | 105 | 89 | 85 | |
| p <0.01 | <0.01 | | <0.01 | <0.01 | | <0.01 | <0.001 | <0.01 | <0.01 | | |

ICDH = Isocitrate dehydrogenase. HBDH = alfa hydroxybutyrate. LDH = lactate dehydrogenase. B = basal. F= final. 2M = two months control. 4M = four months control.

Stimulation of aerobic and anaerobic paths are observed until last control.

## Serie B

## Late Potencials

In one patient late potencials were present before the program. At the end of four months, such abnormalities dissapeared. In other one, who was borderline, late potencials became clearly normal. Table 6.

TABLE 6. Coronary Rehabilitation with high altitude simulated Hypoxia

| LATE POTENCIALS ON SIGNAL - AVERAGED ECG | | | | | | |
|---|---|---|---|---|---|---|
| SUBJECT No. (Age) | TOTAL QRS DURATION-FILTERED (>114 m.s.) | | DURATION OF HFLA SIGNALS (>38 m.s.) | | RMS VOLTAG TERM 40 m.s. (<20 m.s.) | |
| | PRE | POST | PRE | POST | PRE | POST |
| 1 (39) | 126 | 107 | 38 | 17 | 18 | 43 |
| 2 (44) | 113 | 104 | 36 | 29 | 25 | 31 |
| 3 (45) | 120 | 119 | 48 | 31 | 20 | 26 |
| 4 (54) | 98 | 99 | 21 | 23 | 78 | 53 |
| 5 (56) | 94 | 97 | 19 | 22 | 59 | 56 |
| 6 (61) | 100 | 100 | 15 | 18 | 67 | 56 |
| 7 (63) | 104 | 103 | 38 | 39 | 34 | 26 |
| 8 (67) | 113 | 114 | 32 | 32 | 37 | 35 |
| MEAN 54 | 108 | 105 | 31 | 26 | 42 | 41 |
| P | NS | | NS | | NS | |

HFLA = Low amplitud signal duration. RMS = root = mean square voltage in terminal 40 miliseconds. NS = no significant.

Tendency to show better performance in all three parameters. Althoug, no satistcally diferences were found.

## Discussion

## Myocardial Ischemia. Atrial and Ventricular Premature Contractions

Lessening myocardial ischemia and atrial and ventricle premature contractions were found. This are probably due to adenosine effect (Lerman 1990; Muñoz et al 1984; Di Marco et al 1985). This metabolit, is controlled by Pa $O_2$ (Amsterdam and Mason 1977; Fox et al 1974: Berne 1974). High adenosine could increase coronary flow, and might controls heart arrythmia too.

During extreme altitude (6,500 – 8,2000 m), myocardial ischemia and arrythmia was mentioned (Westphal et al 1994), although myocardial contractility is well maintained at 8,000 m (West 1993). Our patients, goes no further than 5,000 m therefore, were not exposed to critical altitude 7,000 – 8,000 m (Hulleman 1978; Horbein 1996; Kayser et al 1992).

## Late Potencials Signal – averaged electrocardiographic (SAECG)

Late potencials (LP), exits (Breithardt, et al 1991), in any specific case if 2 of the 3 following parameters are present: total QRS duration-filtered (> 114 ms) low amplitude signal duration (> 38 ms) and root-mean square voltage in terminal 40 ms (< 20 uV).

In two of five patients with abnormal SACG, this became normal. In the remaining cases, tendency to show better SAECG were found. Outcome of LP could be related to improvement of retard ventricular activation (Gomez et al 1989) and successful coronary perfussion Boeherer et al 1992; Ragosta et al 1993). In both cases, could be

associated to adenosine increment due to hypoxia (Amsterdan and Mason 1977; Fox et al 1974; Berne 1974).

## Hypoxia.Coronary Flow. Myocardial Perfussion. Molecular Biochemistry

Coronary flow/myocardial perfussion, are each another close associated to metabolic myocardium requirements (Amsterdam and Masson 1977). This mechanism works under several stimulus such hypoxia, (Amsterdam and Masson 1977; Fox et al 1974; Berne 1974;Kaijser, Grubbstrom and Berglund 1996). Acute low PO2 at myocardium it will increase coronary flow (Amsterdam and Masson 1977; Fox et al 1974, Berne 1974; Grover 1993). This should occurs, by adenosine production (Amsterdam and Masson 1977; Fox et al 1974; Berne 1974). Other events precipitated by H might also take place. Relaxation of smoth muscle and endothelium cells should be achaived by cellular increasing of guanosin 3', 5' – cyclic monophosphate (cGMP) (Star 1993; Furchgott and Zawadki 1980; Kukreja and Hess 1992) or adenosine 3'5' c y clic monophosfate (c AMP) concentration (Westendorp et al 1992; Sun et al 1996. This two second messengers are related to nitric oxide (NO), endotelium derived relaxing factor (Star 1993; Furchogt and zawadki 1980; Kukreja and Hess 1992) and to adenosine triphosfate (ATP). (Villavicencio 1993) respectively. Thus, the NO results from adenine nucleotides (ATP) (Star 1993), and ATP increases by hypoxia. In relation with NO, nitrix oxide synthase (ONS), also goes up under hypoxia (Arregui 1996).

Plasma atrial natriuretic peptide (ANP), can also be associated with cGMP level (Westendorp et al 1993). Widespread results exists respect to ANP, and hypoxia (Richalet et al 1991; Antezana et al 1994). Report resembling H protocol – for other purposses – shows increment of ANP (Westendorp et al 1993) as well as on rest at high altitude (Milledge 1994).

## Pheripherial or Central Improvement

To stablish frontiers between pheriphery and central improvements by biochemistry findings in the present study is not easy.

Recovery of heart function by left ventricle shortening, ejection fraction, and myocardial perfussion utilizing HCHH to rehabilitate coronary patients should indicate that central rather than pheripheral improvements could be most important. (Marticorena and Marticorena 1994; Marticorena et al 1995; Marticorena et al 1995).

## Follow up Recovery Findings: Myocardial Perfussion. Biochemistry

Endothelial cells and smoth muscle vessels, when are stimulated by H, could remain in such a new condition for some time. This responses resembles, what is seen in fragile respiratory changes due to exposure to high altitude. (Muza et al 1994) found for example, that augmentation of hypoxic ventilatory chemosensitivity persist at least for one week following descent.

## Group Controls

According investigation nature, the observed patients, can be their own control (Niebauer et al 1994). This should be the present case. Two circumstances could be discussed around this point:

**a) Hypoxia: Specific Stimulus**

Changes from basal control ant those in between, are both significantly different compared with basal stage. All controls did move to only one pattern. Therefore, it can not be circumstantial or unrelated findings either. On contrary, looks, as a consisting responses, probable due to hypoxia.

Hypoxia can improve physical training (Gippenreiter and Suslow 1996; Hoppler 1996). Intracellular signals can be initiated by hypoxia. (Webster and Nanette 1996). Physiological and biochemical H changes are inclusive, sensitive to selection in different lineage (Hochachka 1996) Intermittent H exposures shows changes in between central and chronic H exposure (Jalil et al 1996).

All this mechanisms, are matter of interpretation when is applied to any H research line, like the present investigation. Is telling us also, that the importance of H is similar to hyperoxia. Hypoxia and hyperoxia can be good or bad. It can give us health or disease. Even can kill us. It will depends only, how we use them.

**b) Rehabilitation: Stage Patients**

Patients in both series were over three years average after coronary bypass. Spontaneous recovery after such period of time is unlikely. Its ocurrs usually within the first three to four months after surgery (Oldenburg et al 1995).

## Posibilities to use simulated hypoxia technique

The simulated H technique can be applied as an alternative procedure of the natural H system. Both procedures, however are under specific modalities. This is in relation with degree, limit of time and frequency of H exposure, etc. therefore, this technique can not be generalized to other altitudes, over 5,000 m for example.

## Current Indications

Limitations to practice physical exercise due to muscular-skeletal diseases.
Exercise training can not be desirable in various circunstances: in patients with myocardial ischemia, $O_2$ demand is not reduced with exercise training (Digenio, Avril-Slaving and Daly 1996). Training in patients with angina at 100% of ischemia level is not beneficial and the functional capacity may even get worse (Sainz et al 1996).

## Possible Future Indications

Unestable angina
Severe arrythmia
Critical low ejection fraction
Reperfussion syndrome due to angioplasty, coronary bypass, trombolysis, or any conditions increasing free radicals or antioxidants depletion. Insclusive, hypoxia can increase antioxidants level (Sandoval et al 1996;Krasyuk, Beloshitsky and Povstynan 1996).

## Possible Limitations

High sensitivity to hypoxia at the brain (Horbein 1996; Garrido et al 1995) or lungs level.

Severe Cor pulmonale.
Brain severe circulatory impairment.
Sickle cell.

## ACKNOWLEDGMENT

This investigation was supported in the part by CONCYTEC. We are in debt to Ruth Fitzmaurice Pereyra, Herbert Gutiérrez, Pedro Castillo, Juan Silvera, José Yarasca, and Segundo Chang for their technical assistant.

## REFERENCES

Adams H (1963) Adenosine 5' -Triphosphate. Determination with Phosphoglycerate Kinase. In: Methods of Enzymatic Analysis. HU Bergmeyer, edited by Academic Press New York. p539-543.

Amsterdam EA and Mason DT (1977) Coronary artery disease: pathophysiology and clinical correlations. In Exercise in Cardiovascular Health and Disease, edited by Amsterdam EA. Wilmore JH, De Maria AN, New York, EEUU: York Medical Books, p13-34.

Antezana AM., Richalet J-P., Noriega I., Antezana G (1994) Hormonal changes in high altitude natives. First World Congress of High Altitude Medicine and Phisiology, La Paz Bolivia, Abst. p78.

Arreguia (1996) The Brain at high altitude: the clinical problem and the experimental aproaches. Acta Andina Vol V (2), 57-58.

Berne RMC (1974) The Coronary Circulation. In The Mammalian Myocardium, edited by Langer G, Brady A, New York, EEUU: John Wilet & Sons, p 251-281.

Boeherer., Gladmann DB., Lancet RA., et al (1992) Effect of coronary angioplaty on late potencials one to two weeks after acute myocardial infraction (1992) Am J Cardiol. 70:1515-1519.
Breithardt T G., Cain M., El-Sherif N., et al (1991) Standars for Analysis of ventricular late potencials using high-resolution or signal-averaged electrocardiography, J.AM. Coll. Cardiol. 17: 999-1006.

Deedwania PC and Carbajal E (1992) Valoración mediante electrocardiografia ambulatoria de pacientes con arteriopatía coronaria asintomática, inestable y estable en cuanto a isquemia miocardica. In Clinicas Cardiológicas de Norteamerica. Electrocardiografía ambulatoria. Conceptos clinicos actuales, edited by Crawford MH and Keneddy HL, Mexico: MC Graw-Hill, p423-237.

Digenio AG., Avril-Slaving L., Daly JE (1996) Physiological responses to exercise training in patients with silent and symptomatic myocardial ischemia. VI World Congress of Cardiac Rehabilitation. Buenos Aires, Argentina Resumen 36.

Dimarco J., Seller DT., Greenberg ML., et al (1985) Diagnostic and therapeutic use of adenosine in patients with supraventricular tachyarrhytmias. J. Am. Cardiol. 6:417-425.

Fox A.C., Reid GE., Glassman E, et al (1974) Release of adenosine from human hearts during angina induced by rapid atrial pacing. J. Clin. Invest. 53: 1447-57.

Furchgott RJ., Zawadki JV (1980) The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine, Nature 288:373-376.

Garrido E., Segura R., Capdevila A., et al (1995) New evidence from magnetic resonance imaging of brain changes after climbs at extreme altitude. Eur. J. Appl. Physiol. 70: 477-481.

Gippenreiter YB., Suslov FP (1996) Sports training at moderate altitude as an efective means to enhance specific working capacity at sea level. Acta Andina Vol V (2) 24.

Gomez JA., Winters SL., Martisons M., et al (1989). Tha prognostic significance of quantitative signal-averaged variables relative to clinical variables, site of myocardial

infarction, ejection fraction and ventriculare premature beats: a prospective study. J Am. Coll. Cardiol. 13:377-384.

Grover RF (1993) Is hig altitude a risk factor for patients with coronary heart disease? In Hypoxia: Investigaciones Basicas y Clinicas, edited by León Velarde F and Arregui A, Lima Perú IFAE & UPCH, p243-248.

Hochachka PW (1996) Evolution of hypoxia tolerance: diving pinniped model and human hypobaric hypoxia model. Acta Andina Vol V (2) 52.

Hoppler H (1996) Permanent and intermitent hypoxia as reponse modifiers of skeletal muscle tissue with exercise training. Acta Andina Vol V (2) 24-25.

Horbein TF (1996) What's left of the brain after high altitude? Acta Andina Vo. (2) 59.

Hulleman KD (1978) Medicina sportiva: clinica e práctica, editor Pedagógica e Universitaria Ltda., Sao Paulo, Brasil p57.

Jalil JE., Casanegra P., Braun S., et al (1996) Human adaptation to long term, intermitent hypobaric hypoxia. Acta Andina Vol V (2) 76.

KaijserL., Grubbstrom J., Berglund B (1996) Coronary blood flow and myocardial metabolism at simulated altitude. Acta Andina Vol V (2) 11.

Kayser B., Acheson K., Decompaz J., et al (1992) Protein absortion and energy digestibility at high altitude J. Appl. Physiol, 73:2425-2431.

Krasyuk A., Beloshitsky P., Povstyuan A (1996) Mechanism of adaptation to extreme altitudes. Acta Andina Vol V (2) 25.

Kukreja R., Hess ML (1992) The Oxygen radicals system: from equations through membrane-protein interactions to cardiovascular injury and protection. Cardiovascular Research 26: 641-655.

Lerman BB (1990) Electrophysiologycal basis for the use of adenosin in the diagnosis and treatment of cardiac arrhytmias. Br. Heart J. 63:3-4.

Marticorena EA (1984-85) Nueva técnica en rehabilitación cardiaca y prevención primaria coronaria: utilización de las grandes alturas. Arch. Inst. Biol. And. 13:189-206.

Marticorena EA and Marticorena JM (1990) Cornary Prevention and Rehabilitation Utilizing High Altitude, edit. SAGSA, Lima Perú.

Marticorena EA et al (1993) Rehabilitación Cardiaca por medio de grandes alturas para coronarios con puenteo. In Tratado de Cirugía, edited by Romero Torres R, Mexico, Interamericana p962-966.

Marticorena EA (1993) Montañismo médico: rehabilitation de pacientes coronarios con bypass. Rev. Peruana de Cardiología 29: 25-29.

Marticorena EA., Fernández-Dávila L., Zamora C., et al (1993) Prevención coronaria: uso de la altura simulada con cámara hipobárica, XIV Congreso Peruano de Cardiología, Lima Perú. Resumen p17.

Marticorena EA., Marticorena JM., Contreras Gonzalez A. et al (1994) Cardiac Rehabilitation of coronary bypassed patients natural and simulated high altitude techniques. First World Congress of High Altitude Medicine and Physiology. La Paz, Bolivia, Abst. p101.

Marticorena EA., Marticorena JM., Contreras Gonzalez A. et al (1995) Rehabilitación cardiaca con altura simulada de pacientes con bypass coronario. XV Congreso Peruano de Cardiología. Lima Perú. Resumen, p26-27.

Marticorena EA., Marticorena JM., Contreras Gonzales A. et al (1995) Rehabilitación cardiáca con altura simulada (cámara hipobárica) en coronarios con infarto de miocardio y bypass. Rev. Peruana de Cardiolog. 21:7-15.

Muñoz A., Leenhardt A., Sassine A (1984) Therapeutic use of adenosin for terminating spontaneous paroxsysmal supraventricular tachycardia. Europ. Heart J. 5:735-738.

Milledge JS (1994) Fluid and electrolyte balance on going to altitude. First World Congress of High Altitude Medicine and Physiology. La Paz, Bolivia, Resumen p130.

Muza SR., Fulco CS., Lyons T, et al (1994) Augmented chemosensitivity at altitude and after return to sea level: impact on subsequent return to altitude. First World Congress of High Altitude Medicine and Physiology, La Paz, Bolivia, Resumen p111.

Niebauer J., Hambrecht R., Sehlierf G., et al (1994) Five years of physical exercise and low fat diet: effects on progression of coronary artery disease. J Cardiopulm. Rehab. 15: 47-64.

Oldenburg B., Martin A., Greenwood J., et al (1995) Controlled trial of behavioral and educational intervention following coronary artery bypass surgery. J Cardiopulm. Rehab. 15: 39-46.

Ragosta M, Sabia PJ., et al (1993) Effects of late (1 to 30 days) reperfusion after acute myocardial infarction on signal averaged electrocardiogram. Am J Cardiol. 71: 19-23.

Richalet JP., Galen FX., Bouisson P., Rathat C (1991) Atrial natriuretic factor and altitude. International Congress of Mountain Medicine, Abst. 31.

Sainzi., Carrera T, Valenzuela L., et al (1996) Training coronary heart disease patients with angina at 100% of ischemic level. IV World Congress of Cardiac Rehabilitation. Buenos Aires. Argentina, Resumen 213.

Sandoval M., Araneda O., Escobar J., et al (1996) Plasma antioxidant capacity as related to exercise and acute high altitude exposure. Acta Andina. Vol. V (2), 27-28.

Star A (1993) Oxído Nítrico. The Am. J. Med. Sc. 306, No. 5. Nov 1993. In Revista de Revistas, Lima Perú, Vol. 3:27-34.

Sun B., Jung-Ying D., Jiang-Fan Ch., et al (1996) Studies on mechanisms of hipoxic pulmonary hypertension. Acta Andina Vol V (2) 36-37.

Villavicencio M (1993) Bioquímica. Lima Perú: A&B Editors. p 264.

Webster KA., Nanette H (1996) Models of heart disease: early and late gene responses to hypoxia, ischemia and reoxygenation. Acta Andina Vol V (2) 53.

West JB (1993) Human tolerance to extreme altitude. In hypoxia: Investigaciones Básicas Clínicas, edited by León Velarde F and Arregui A. Lima-Perú. IFEA & UPCH. p227-241.

Westphal K., Lischke V., Treibel W. et al (1994) Prevention of cardiovascular complication in extreme altitude mountaineering (Kilimanjaro 5895m and Mt. Everest 8848m) Analysis by holter ambulatory ECG. First World Congress of High Altitude Medicine nad Physiology. La Paz, Bolivia Abst. p106.

Westtendorp RGJ., Drajer R., Meindres AE, et al (1992) Cyclic GMP-mediate dicrease in permeability of human endothelial cell monolayers. In Atrial Natriuretic Peptide a Modulator of Pulmonary Pathoplysiology, edited by Westerdorp RGJ, Leinden, The Netherlands, J Bout & zonen. p47-63.

Westtendorp RGJ., ROSS AN., vd Hoeven HG., et al (1993) Atrial Natriuretic peptide improves pulmonary gas exchange in subjects exposed to hypoxia. In Atrial Natriuretic Peptide a Modulator of Pulmonary Pathophysislogy, edited by Westerdorp RGJ, Leinden, The Netherlands J Bout & Zonen, p91-105.