Improvement of myocardial perfusion in coronary patients after intermittent hypobaric hypoxia

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Background. **Persons living at high altitude (exposed to hypoxia) have a greater number of coronary and peripheral branches in the heart than persons living at sea level. In this study we investigated the effect of intermittent hypobaric hypoxia on myocardial perfusion in patients with coronary heart disease.**

Methods and Results. **We studied 6 male patients (aged ≥53 years) with severe stable coronary heart disease. All patients were born at sea level and lived in that environment. They underwent 14 sessions of exposure to intermittent hypobaric hypoxia (equivalent to a simulated altitude of 4200 m). Myocardial perfusion was assessed at baseline and after treatment with hypoxia by use of exercise perfusion imaging with technetium 99m sestamibi. After the sessions of hypoxia, myocardial perfusion was significantly improved. The summed stress score for hypoperfusion, in arbitrary units, decreased from 9.5+ to 4.5+ after treatment ($P = .036$). There was no evidence of impairment of myocardial perfusion in any patient after treatment.**

Conclusions. **Intermittent hypobaric hypoxia improved myocardial perfusion in patients with severe coronary heart disease. Though preliminary, our results suggest that exposure to intermittent hypobaric hypoxia could be an alternative for the management of patients with chronic coronary heart disease. (J Nucl Cardiol 2006;13:69-74.)**

Key Words: Myocardial perfusion • angiogenesis • hypoxia • altitude • coronary patient

Persons living at high altitude have a greater number of coronary and peripheral branches in the heart than persons living at sea level.[1] It has been reported that there is a more efficient generation of cellular adenosine triphosphate at high altitude than at sea level.[2] These findings together could explain the lower prevalence of coronary diseases reported at high altitude.[3]

It is known that ischemic and hypoxic preconditioning triggers myocardial angiogenesis in experimental conditions.[4-7] Studies in animals have shown that adaptation to hypoxic/ischemic preconditioning provides heart protection against acute ischemic injuries.[8,9] We have demonstrated that intermittent hypobaric hypoxia increases nitric oxide levels in serum from coronary patients and this increase remained higher than baseline level even 3 months after the sessions of hypoxia were finished (unpublished data, 2002).

Because one of the goals in the treatment of coronary artery disease (CAD) is to restore myocardial perfusion, we investigated the effect of intermittent hypobaric hypoxia on myocardial perfusion in patients who were living at sea level with severe coronary heart disease.

METHODS

Subjects

We studied 6 male subjects (aged ≥53 years) with severe stable coronary heart disease without any possibility of further surgical interventions (Table 1). All subjects underwent treatment in the Hospital Central of Aeronáutica, Peruvian Air Force, Lima, Peru. All were born at sea level and lived in that environment. Some of them had a previous history of exposure to hypobaric hypoxia, either natural (in high lands above 3000 m) or simulated (in chambers

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Table 1. Basal features of 6 coronary patients exposed to intermittent hypobaric hypoxia during 14 weekly sessions in a hypobaric hypoxic chamber (simulated altitude of 2400–4200 m)

Patient	Age (y)	HR (beats/min)	BP (mm Hg)	Angina	MI	SH	PVD	Nitrates	Calcium antagonists	β-Blockers	No. of CABG	No. of angioplasties	Pacemaker	Previous NHH	Previous SHH
A	68	64*	110/60	–	+	+	+	+		+	2	–	–	1	5
B	80	76	120/70	–	–	–	–	+	+	–	1	–	–	–	–
C	64	76	130/80	–	–	+	–	–	–	+	2	5	–	1	3
D	53	72	130/85	+	+	+	–	+	–	+	1	–	–	–	1
E	76	67	135/75	–	–	–	+	+	+	–	1	–	+	–	–
F	69	60	130/70	–	–	+	–	+	+	–	1	–	–	1	3

HR, Heart rate; *BP*, blood pressure; *MI*, myocardial infarction; *SH*, systemic hypertension; *PVD*, peripheral vascular disease; *CABG*, coronary artery bypass graft surgery; *NHH*, number of exposures to natural hypobaric hypoxia; *SHH*, number of exposures to simulated hypobaric hypoxia.
*Patient with chronic atrial fibrillation.

mimicking high-altitude conditions) (or both). They followed a specific program of exposure to intermittent hypobaric hypoxia previously tested by our group.[10] Patients maintained their usual medication during the study period. All patients gave informed consent before enrolling. The study design was approved by the ethical committee of the Hospital Las Palmas, Lima, Peru.

Hypobaric Chamber

We used a multi-place hypobaric chamber designed for 8 subjects (Kinney Vacuum Company, Mass [transferred to the Hospital Las Palmas from the US Air Force]). The patients followed a program of exposure to simulated intermittent hypobaric hypoxia based on 14 sessions of progressive ascent on a weekly basis. The program started 6 months after coronary bypass surgery was performed in the patients. Every session was based on an exposure to hypoxia of 4 hours. The first 2 hours consisted of a progressive ascent starting at sea level, the third hour (plateau) was defined according to the session number, and the fourth hour consisted of a progressive descent to sea level. The first session was programmed to reach 2400 m (plateau), with a 250- to 300-m increase in the following sessions until a peak of 4200 m (from session 10 to the end) was established. During the hypobaric stay in the chamber, subjects were asked to stay seated for all experiments.

Exercise Perfusion Imaging

Baseline myocardial perfusion was assessed a few days before the program of hypobaric hypoxia was started. The post-treatment control was done 6 months after the last session of hypoxia.

One-day rest/stress Tc-99m protocol. The same-day rest/stress approach allowed the entire study to be completed within 5 to 6 hours. The standard doses given were 8 mCi (296 MBq) for the rest study and 22 mCi (814 MBq) for the exercise study. Every patient was instructed to ingest a light-fatty meal, 30 minutes after injection, to promote tracer clearance from the gallbladder. Rest images were taken 1 hour after injection, at an interval of 3 hours between the rest and stress injections. Exercise testing was performed with a computerized unit (Marquette Centra; Marquette, Milwaukee, Wis). The level of the exercise test was at least 85% of the maximum heart rate predicted for each patient. Exercise was continued for 1 to 2 minutes after injection of technetium 99m sestamibi.[11]

Acquisition protocol. We used a collimator with high resolution and a circular 180° orbit. The acquisition consisted of 64 projections beginning at 45° at the right anterior oblique position.

Reconstruction protocol. We used the CEqual quantitative method (Cedars-Emory quantitative analysis). Myocardial perfusion was assessed with a gamma camera (GE Millennium MPR; GE Healthcare, Milwaukee, Wis).

Interpretation of perfusion imaging. Twenty-nine myocardial segments were defined[12] and were scored by use of a system (hypoperfusion) based on plus signs: +, very mild ischemia; ++, mild ischemia; +++, moderate ischemia; and ++++, severe ischemia. For each patient, a summed stress score (in arbitrary units) of hypoperfusion was used to assess the effect of intermittent hypobaric hypoxia on myocardial perfusion.

Statistical Analysis

The Wilcoxon matched-pairs test was used to estimate the P value. $P < .05$ was considered statistically significant.

RESULTS

After 14 sessions of intermittent hypobaric hypoxia, myocardial perfusion was improved in patients with severe chronic coronary heart disease (Table 2). The summed stress score decreased from 9.5+ to 4.5+ after treatment ($P = .036$, Wilcoxon test).

In patient A, who had a history of 2 coronary bypass surgeries and exposure to hypoxia (Table 1), the moderate ischemia observed at anterior segment 20 was improved, yielding normal perfusion after the hypoxia sessions (Table 2). In 2 patients without a history of hypoxic exposure, their very mild ischemia was also improved. Furthermore, although in some segments the hypoperfusion was not improved, we did not observe any impairment in myocardial perfusion after the intermittent hypobaric hypoxia, as noted in Figure 1.

During the treatment under hypoxic conditions, the sessions inside the chamber were well tolerated by all patients. None of them had angina develop or showed relevant symptoms to discontinue the treatment.

DISCUSSION

Our findings showed a significant enhancement of myocardial perfusion in patients with coronary heart disease after following a program of intermittent hypobaric hypoxia. To our knowledge, this is the first study showing an improvement in myocardial perfusion after exposure to intermittent hypoxia in CAD patients. It has been reported previously that very acute exposure to hypoxic conditions increases the myocardial blood flow in healthy subjects[13] and in CAD patients.[14] Now, we provide evidence that intermittent hypobaric hypoxia improves myocardial perfusion in severe stable chronic CAD patients and that this improvement is present 6 months after the exposure to hypoxia is completed. These findings indicate that the benefits of intermittent hypobaric hypoxia on myocardial perfusion may remain for a prolonged period of time.

We started the program of intermittent hypobaric hypoxia 6 months after coronary bypass surgery was performed in the patients because it is known that a spontaneous recovery of perfusion can occur within the first 4 months after surgical treatment.[15]

The post-treatment evaluation was performed 6 months after the last session of hypoxia based on our previous observations that serum nitric oxide concentrations remained higher than baseline levels several months after the exposure to hypoxia was finished under the same conditions (unpublished data, 2002). Experimentally, it has been reported that the cardioprotective effect of chronic hypoxia on rabbit hearts persists for long periods as well and is associated with an increase in the activity of nitric oxide synthase.[16]

In our study all patients showed enhancement of myocardial perfusion after the program of intermittent hypobaric hypoxia. We did not observe any impairment of myocardial perfusion. These findings could explain the clinical improvement found in CAD patients who underwent programs of natural or simulated intermittent hypoxia.[10,17-20]

Two mechanisms could explain, at least in part, the improvement in myocardial perfusion found in our study. The first mechanism is vasodilatation of coronary arteries. Nitric oxide is one of the main molecules responsible for vasodilatation.[21] It has been reported that hypoxia increases the production of serum nitric oxide in rats[22] and in human beings.[19] In addition, it has been demonstrated that L-nitroarginine, a blocker of nitric oxide synthase, completely abolishes the increase in myocardial blood flow induced by hypoxia in fetal lambs.[23]

Another mechanism that could be involved in the effect produced by hypoxia on myocardial perfusion is the process of angiogenesis. The effect of hypoxia on angiogenesis has been extensively studied in vitro[4,24] and in animal models in vivo.[4,7] Hypoxia increases the production of vascular endothelial growth factor,[25-27] the most potent angiogenic factor, and many other angiogenic factors as well.[28,29] Although vasodilatation and angiogenesis could explain our findings according to experimental studies, the role of hypoxia in angiogenesis and vasodilatation in human beings deserves extensive research.

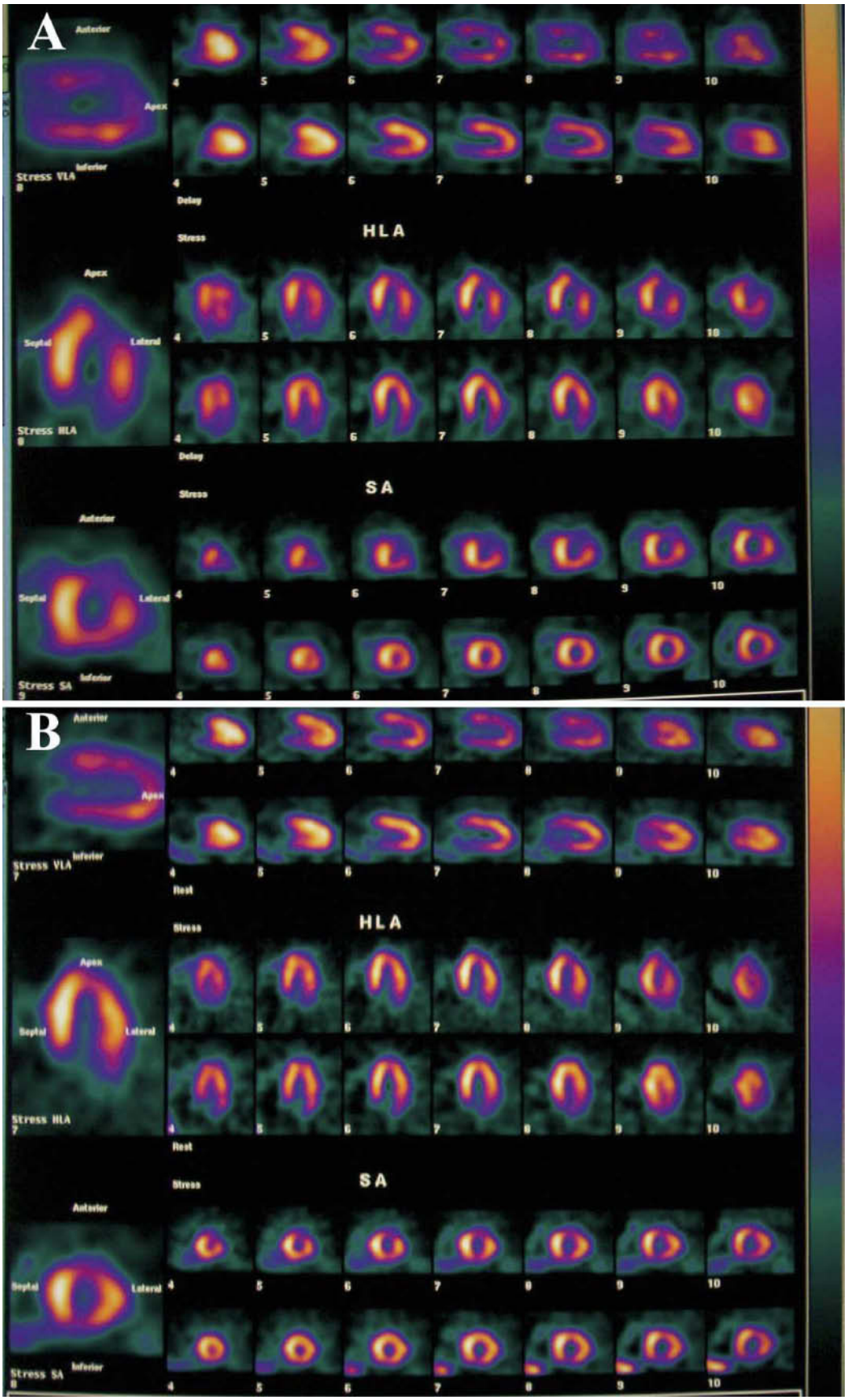
In conclusion, intermittent hypobaric hypoxia improved myocardial perfusion in patients with severe stable CAD. There was no evidence of impairment of

Table 2. Myocardial perfusion in 6 coronary patients exposed to intermittent hypobaric hypoxia

	Patient											
	A		B		C		D		E		F	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Segment												
1							++				+	+
2												
3												
4	–	–					++	+				
5												
6											++++	
7							++				++	+
8												
9												
10	–	–			+	+	++	++				
11												
12												
13											+	+
14												
15												
16	–	–			++		++	+				
17									+			
18			+									
19												
20	+++										++	+
21	++	+									++++	++
22	–	–					+++					
23	–	–					++					
24			+	+	+++	+	++++	+++				
25	++	++										
26												
27	++	++					++++	+			+++	++
28									+	+		
29												
Hypoperfusion	9+	5+	2+	1+	6+	2+	23+	8+	2+	1+	17+	8+

Hypoperfusion was scored as follows: +, very mild ischemia; ++, mild ischemia; +++, moderate ischemia; and ++++, severe ischemia. The minus sign denotes the absence of tracer uptake. Segments with normal perfusion do not have any mark. Cardiac segments are represented by the following numbers: 1, 7, 13, and 20—anterior; 2, 8, and 14—anteroseptal; 3, 9, and 15—inferoseptal; 4, 10, and 16—inferior; 5, 11, and 17—inferolateral; 6, 12, and 18—superolateral; 19—anterobasal; 21—anteroapical; 22—inferoapical; 23— inferior; 24—inferobasal; 25—proximal septal; 26—distal septal; 27—apical; 28— distal lateral; and 29—proximal lateral.
PRE, Before intermittent hypobaric hypoxia, *POST,* after intermittent hypobaric hypoxia.

Figure 1. Exercise perfusion imaging with Tc-99m sestamibi of patient F after a program of intermittent hypobaric hypoxia. **A**, Pre–intermittent hypobaric hypoxia image showing severe hypoperfusion at the anterior, anterolateral, lateral, apical, and anteroapical segments. There was significant transitory ventricular dilatation with exercise. **B**, Post–intermittent hypobaric hypoxia image showing moderate hypoperfusion at the anterior, anterolateral, and apical segments. There was mild hypoperfusion at the anteroapical segment. There was no evidence of left ventricular dilatation. Characteristics of the patient are detailed in Table 1. *HLA*, Horizontal long axis; *VLA*, vertical long axis; *SA*, short axis.


A
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Inferior
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Anterior
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Rest
HLA
Stress
Apex
Septal
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myocardial perfusion in any patient. Though preliminary, our results suggest that exposure to intermittent hypobaric hypoxia could be an alternative for the management of patients with chronic coronary heart disease.

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