MIBG Scintigraphic Assessment of Cardiac Adrenergic Activity in Response to Altitude Hypoxia

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High altitude hypoxia induces a decrease in the cardiac chronotropic function at maximal exercise or in response to isoproterenol infusion, suggesting an alteration in the cardiac sympathetic activation. Iodine-123 metaiodobenzylguanidine ([^{123}I]MIBG) was used to map scintigraphically the cardiac sympathetic neuronal function in six male subjects (aged 32 ± 7 yr) after an exposure to high altitude that created hypoxic conditions. Results obtained just after return to sea level (RSL) were compared with the normal values obtained after 2 or 3 mo of normoxia (N). A static image was created as the sum of the 16-EKG gated images recorded for 10 min in the anterior view of the chest at 20, 60, 120, and 240 min after injection. Regions of interest were located over the heart (H), lungs (L), and mediastinum (M) regions. There was a significant decrease in the H/M and the L/M ratios in RSL compared to N condition. Plasma norepinephrine concentration was elevated during the stay at altitude but not significantly different in RSL compared to N. In conclusion, cardiac [^{123}I] MIBG uptake is reduced after an exposure to altitude hypoxia, supporting the hypothesis of an hypoxia-induced reduction of adrenergic neurotransmitter reserve in the myocardium. Furthermore, the observed significant decrease in pulmonary MIBG uptake suggests an alteration of endothelial cell function after exposure to chronic hypoxia.

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Previous studies have shown that exposure to altitude hypoxia induces striking abnormalities of the autonomic nervous system. The cardiac chronotropic response to maximal exercise or to isoproterenol infusion has been found severely decreased in acute, subacute or chronic hypoxia (*1–3*). Hypoxia induces an increase in plasma catecholamine concentrations at rest and exercise (*3–5*). These observations suggest that the response of the cardiac beta adrenergic receptors is damped in hypoxia. This decrease in the response to an adrenergic stimulation could be the result of, among other mechanisms, a down-regulation in the number of beta receptors at the postsynaptic level or an alteration in the norepinephrine or kinetics in the myocardium, at the presynaptic level. The present study was undertaken to explore the second hypothesis, i.e., an hypoxia-induced decrease in the uptake, storage or turnover of norepinephrine within the myocardial nerve terminals using iodine-123 metaiodobenzylguanidine ([^{123}I]MIBG) scintigraphic imaging.

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MATERIAL AND METHOD

Study Population

Six normal male sea level natives, aged 32 ± 7 yr volunteered to enter into the study. Clinical and electrocardiographic examination were performed to assess cardiac integrity. Subjects were medical students, doctors, or scientists and gave their fully informed consent to participate in the study.

Subjects were involved in an extensive medical study at the "Observatoire Vallot" (Mont-Blanc, Chamonix) at 4350 m of altitude. They remained in the hypoxic conditions of altitude during 8 days. On the eighth day, blood samples were drawn at rest for catecholamine concentration measurements (H8). On the ninth day, the subjects were rapidly transferred to Orsay (altitude = 20 m) by helicopter (10 min) then car (1 hr) and plane (2.5 hr at the altitude of 3000–3500 m in a nonpressurized cockpit to preserve hypoxic conditions).

Data Acquisition

The scintigraphic MIBG studies started 2 to 5 hr after the return to complete normoxia. A control MIBG scintigraphy was performed in normoxia 2 to 3 mo later. In the two conditions of return to sea level (RSL) and normoxia (N) the methodology was identical. Thyroid blockage was performed with a standard lugol procedure. A small catheter was inserted into an antecubital vein. After a 30-min resting period, a venous blood sample was drawn for the measurement of plasma norepinephrine (NE) and epinephrine (E) concentrations. [^{123}I]MIBG was then intravenously infused at the dose of 3–4 mCi.

An ECG-gated acquisition was performed with 16 frames per cardiac cycle in 64 × 64 matrix format, in the anterior

view of the chest during 10 min at 20, 60, 120, and 240 min after injection. A raw static image was immediately created by summing the 16 images of the dynamic series. Each volunteer was studied on the same gamma camera (either Siemens ZLC 75 or GE 400 T) and the data were recorded on a Sopha S 4000 Computer.

Data Processing

After median filtering of the series of 16 images, a first harmonic Fourier analysis was performed in order to produce an amplitude image helpful for the localization of myocardial motion. The end systolic image was visually selected by the operator looking at the cinematic display of the filtered series of images. On this end systolic image, the myocardial activity is best separated from both left lung and liver activities. Using a four-quadrant TV display of ED, ES, amplitude and raw static images (Fig. 1), 7 × 7 pixels regions of interest (ROIs) were displayed on the four quadrants and placed manually over the heart, the upper mediastinum and the upper lungs. The heart to mediastinum (H/M) and the lung to mediastinum (L/M) ratios were computed over the raw static image. The vertical distance from the mediastinal and pulmonary ROIs to the cardiac ROI was identical for each scintigraphic study in the same subject.

RESULTS

H/M, and L/M ratios at the different imaging times, NE and E plasma concentrations are shown respectively in Table 1 and Table 2. The variance analysis, taking into account the two conditions of RSL and beta, reached significance with $p < 0.01$ for both pulmonary and cardiac MIBG uptake. The variance analysis did not find a significant influence of the time (20, 60, 120, 240 min) on the results. The statistical significance between the two conditions was then assessed for each time point by paired t-tests. Following the stay at high altitude, MIBG uptake was modified, compared to normoxic basal conditions. In essence at each time point, H/M was significantly decreased after RSL study when compared with N study of ~16% ($p < 0.05$ at 20 and 120 min, $p < 0.01$ at 60 min and $p < 0.001$ at 240 min) (Fig. 2). H/M increased from 20 to 240 min during N study and was stable after RSL study. At each time point, L/M was significantly decreased after RSL study when compared with N study (Fig. 2). L/M increased from 20 to 240 min during N study and was stable after RSL study. These data indicate a significant decrease in MIBG cardiac and pulmonary uptake and an alteration of its relative kinetics following the stay at high altitude. Catecholamine concentrations were not significantly different in RSL and N conditions, but norepinephrine concentration was significantly higher at altitude H8 ($p < 0.05$).

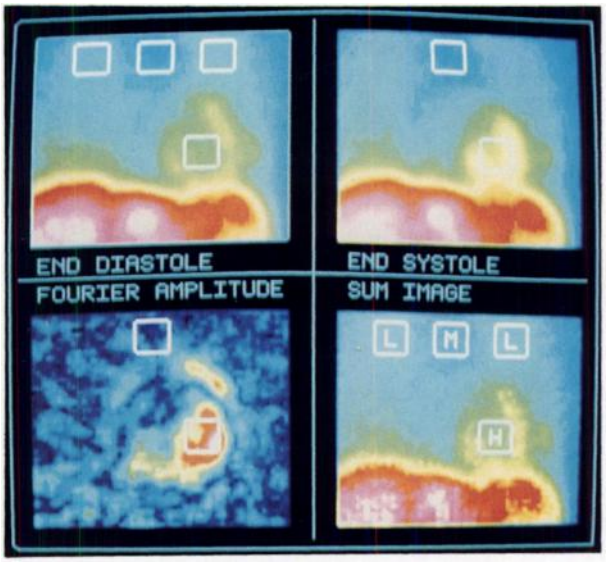

FIGURE 1
MIBG myocardial scintigraphy at 4 hr after injection in the anterior view of the chest. H = heart; L = lung; M = mediastinum.

TABLE 1
Ratios of [^{123}I]MIBG Activity in the Various ROIs in Normoxia (N) and at the Return to Sea Level After an 8-Day Stay at Altitude (RSL)

		H/M	L/M
20 min	N	2.04 ± 0.26	1.76 ± 0.04
	RSL	1.84 ± 0.25*	1.35 ± 0.13‡
	δ (%)	−10	−23
60 min	N	2.12 ± 0.30	1.74 ± 0.04
	RSL	1.88 ± 0.30†	1.37 ± 0.16†
	δ (%)	−11	−21
120 min	N	2.13 ± 0.36	1.65 ± 0.04
	RSL	1.90 ± 0.32*	1.35 ± 0.15†
	δ (%)	−11	−18
240 min	N	2.22 ± 0.36	1.53 ± 0.15
	RSL	1.87 ± 0.34‡	1.33 ± 0.17*
	δ (%)	−16	−13

Comparison to N (n = 6): * $p < 0.05$ paired t-test.
† $p < 0.01$.
‡ $p < 0.001$.
H: Heart, M: Mediastinum, L: Lungs.

DISCUSSION

Metaiodobenzylguanidine radiolabeled with ^{125}I, ^{131}I, or ^{123}I is a norepinephrine competitive inhibitor and

TABLE 2
Norepinephrine (NE) and Epinephrine (E) Plasma Concentrations in ng·ml^{-1} in Normoxia (N), After an 8-Day Stay in Altitude (H8), and After Return to Sea Level (RSL)

	NE	E
N	344 ± 77	59 ± 30
H8	767 ± 375*	48 ± 19
RSL	474 ± 261	85 ± 68

Comparison to N (n = 6): * $p < 0.05$.

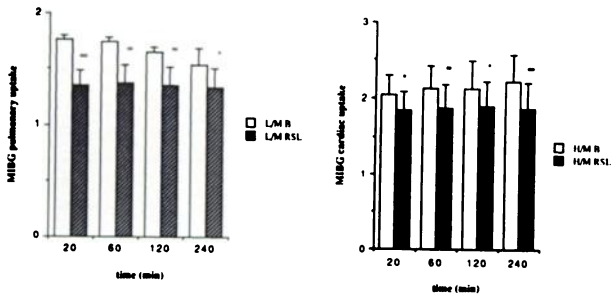

FIGURE 2
Cardiac MIBG uptake (left) and pulmonary MIBG uptake (right) were significantly decreased following the stay at high altitude (RSL) when compared to normoxic basal condition (B). 0: $p < 0.005$ – 00 = $p < 0.01$ – 000 = $p < 0.001$ (paired t-test).

has been formerly used for the management of pheochromocytoma. It is also used in the study of the cardiac adrenergic system and explores the content and the turnover of catecholamine granules in this tissue (*6–10, 15*). It has been demonstrated that MIBG has an uptake mechanism similar to that of norepinephrine in adrenomedullary cells, i.e., a saturable, ATP-dependent, sodium-dependent transport that could be inhibited by desmethylimipramine and cocaine or reserpine (*11*).

Recently, MIBG pulmonary uptake was proposed as a potential marker of endothelial function (*13*). The authors showed that the uptake of MIBG by the rat lung is characterized by Michaelis Menten kinetics, and is inhibited by imipramine, ouabain, hyperkaliemia and hypothermia in a manner similar to that previously described for serotonin or norepinephrine. MIBG appears to have a similar mechanism of lung uptake as biogenic amines: an ATP- and sodium-dependent saturable transport through endothelial cell membrane. They also showed a decrease in pulmonary MIBG uptake in endotoxemia, a pathological model involving endothelial cell lesions (*13*).

The present study was performed to assess the effect of prolonged hypoxia on the myocardial uptake of [^{123}I] MIBG. Because the high altitude laboratory was not equipped with nuclear medicine devices, scintigraphic imaging was done at sea level and the delay between complete return of normoxia and [^{123}I]MIBG injection has been reduced to a minimum of 2 to 5 hr. Thus rapid changes in the adrenergic system following restoration of normoxia could not be monitored but the observation of slower mechanisms could be possible. Previous studies showed that modifications of cardiac chronotropic function may involve slow processes developed in a few days: the heart rate response to isoprenaline infusion decreased when the duration of altitude hypoxic exposure increased from 2 to 4 and 21 days (*2*).

A companion study was performed during the same experimental campaign to explore the cardiac response to isoproterenol (IP) infusion in hypoxia (H8) and after the RSL (*18*). A 35% decrease in chronotropic response to IP was found in H8 in comparison to the normal response. IP infusion realized in RSL, 1 hr after the last myocardial imaging still showed a 21% decrease in cardiac response to IP. Although mechanisms involved are different, since IP infusion explores beta postsynaptic receptors and MIBG scintigraphy intravesicular presynaptic uptake, the magnitude of both alterations was similar. These observations suggest that the decrease in MIBG uptake at RSL is induced by the exposure to altitude hypoxia.

For data quantification we chose H/M and L/M ratios as indexes of myocardial and lung uptake respectively. Because we did not have the opportunity to quantify absolute activity, cardiac count rates had to be normalized. We have normalized with the nonspecific activity of the upper mediastinum, a nontarget area for MIBG. Thus, these H/M and L/M ratios are relative parameters which can be used to evaluate absolute uptake.

The precise mechanism by which [^{123}I]MIBG uptake would be altered by prolonged exposure to hypoxia is not clear. MIBG intravesicular uptake has been shown to be ATP-dependent and might thus be sensitive to the O_2 availability in the myocardium. In the present study, however, the decreased uptake was observed after restoration of normal oxygenation and myocardial ATP levels are not likely to be altered in RSL. An alteration in the "uptake 1" pathway followed by MIBG could account for the observed data, providing that this alteration would involve some slow processes not reversible with rapid return to normoxia. The decrease in uptake rate could also induce an accumulation of NE in the synaptic space and thus favor a down-regulation of the beta receptors. This mechanism of down-regulation has been proposed to explain the hypoxia-induced decrease in the chronotropic response to adrenergic activation (*2,3,14,18*).

In the present study, mean NE and E plasma concentrations were not significantly higher in RSL than in basal condition, but NE level was elevated during the stay in altitude, as shown by H8's significantly higher value. Normal levels of plasma NE and E in our study are not in favor of a competition between catecholamine and MIBG at the presynaptic level. Such a hypothesis was suggested by Nakajo (*8*) who observed an inverse relationship between plasma NE and myocardial MIBG uptake in patients with pheochromocytoma; his hypothesis was supported by a subjective analysis where the heart intensity at 24 hr was visually graded from 0 to 3 depending on the relative uptake of the liver; the plasma catecholamine concentrations were also much more elevated (>1000 pg/ml) in his series than in normal subjects in hypoxic conditions (767 pg/ml). Furthermore, our data are in agreement with the

results of Schofer who did not find a correlation between plasma NE concentration and MIBG uptake assessed by heart to mediastinum ratio in patients with congestive heart failure (*14*).

The lungs are known to actively take up and metabolize circulating biogenic amines (*16,17*). In the present study, the pulmonary uptake decreased during RSL study and the relative kinetics were altered when compared with N. This suggests changes in pulmonary circulation involving an alteration of either vascular surface area or endothelial cell function. This fact could be related to the mechanism of pulmonary edema.

CONCLUSION

Iodine-123 MIBG scintigraphy performed in humans after an 8-day stay at high altitude demonstrated a decrease in myocardial and pulmonary [^{123}I]MIBG uptake. This observation can be related to an hypoxia-induced alteration in the myocardial adrenergic activity and pulmonary endothelial cell function.

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