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Exercise in hypoxia: a model from laboratory to on field studies

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Abstract:	Clinical outcome and quality of life of chronic heart failure (HF) patients have greatly improved over the last two decades. These results and the availability of modern lifts allow many cardiac patients to spend leisure time at altitude. HF per se doesn't impede a safe stay at altitude, but exercise at both simulated and real altitude is associated with a reduction in performance, which is inversely proportional to HF severity. For example, in normal subjects, the reduction in functional capacity is ~2% every 1000 m altitude increase, whereas it is 4% and 10% in HF patients with normal or slightly diminished exercise capacity and in HF patients with markedly diminished exercise capacity. Also the on-field experience with HF patients at altitude confirm safety and shows overall similar data to that reported at simulated altitude. Even "optimal" HF treatment in patients spending time at altitude or at hypoxic conditions is likely different from optimal treatment at sea level, particularly as regards β-blockers selectivity. Furthermore, high altitude, both simulated or on-field, represents a stimulating model of hypoxia in HF patients and healthy subjects. Our data suggest that spending time at altitude (<3500 m) can be safe even for HF patients, provided that subjects are free of co-morbidities that may directly interfere with the adaptation to altitude and are stable. However, HF patients experience a reduction of exercise capacity directly proportional to HF severity and altitude. Finally, HF patients should be tested for functional capacity and undergo a specific "hypoxic-

	tailored treatment” to avoid pharmacological interference with altitude adaptation mechanisms, particularly with regard to the selectivity of beta-blockers.

We thank the Editor and Reviewers for their comments and suggestions. Below is a step by step reply.

Reviewer Comments:

Editor:

The article merits a central figure to show the main message and to enhance its visibility

We thank the Editor for his suggestion. A central figure has been added.

Reviewer #1:

In this research paper, Vignati and colleagues evaluated the current evidence based medicine about pathophysiological adaptation to altitude of patients with heart failure, which is a complex phenomenon that probably takes long more than 3 weeks as reported. Altitude does not just behave as an hypoxic condition that enhances the risk of cardiovascular events, because also atmospheric pressure plays a key role. Finally it emerged that an acute exposure to moderate altitude is safe for patients with heart failure if they keep in mind that they will have a reduction of their functional capacity in the order of 4 to 10%. For this reason, a complete cardiopulmonary assessment (performed at sea level) appears essential to develop an objective clinical opinion.

STRENGTHS
Since the improvement in quality of life of patients with heart failure and the growing availability of reaching high altitude, physicians have to deal with the need of objective answers about the fears of spending a period in the mountains. This paper tries effectively to summarize what to pay attention (e.g. therapy with beta-blockers or previous history of central sleeping disorder) and what to inform the patient about (e.g. the degree of physical activity safely permitted).

We thank Reviewer 1 for their careful review and appreciation of our work.

LIMITS

* **At page 4. There is a repetition of "That that".** The repetition has been deleted.
* **The impact of high altitude (above 3500mt) to HF is still under-investigated.** You are right. We have amended the conclusions to include this consideration.
* **The majority of studies cited have poor numerosity; building a prospective controlled study at high altitude is difficult and really expensive to do.** You are right. We have amended the conclusions to include this consideration.

Reviewer #2:

The review article "Exercise in hypoxia: a model from laboratory to on filed studies" by Vignati et al. focusses on the effects of high altitude on cardiopulmonary physiology, and pathophysiology, with regard to heart failure (HF). It gives a fascinating overview on the methodological approach towards studying these effects, the different methods in the lab and field studies in the mountains, and the efforts performed within the past years. It becomes obvious that this field of research is very demanding from a methodological, but also from a logistical and resource standpoint. Nevertheless, it becomes clear that the research in this field is successful and that important insight could be gained from these studies.

The enthusiasm of the group is clearly visible. The article is well written and reflects the current state of knowledge in the field. The cited literature is adequate. It is a very comprehensive but still concise review on the topic, that may be of great interest to readers of this journal.

We thank Reviewer 1 for their careful review and appreciation of our work.

Major Comments:

- The article has an emphasis on the Monzino research group's contributions to cardiopulmonary adaptations at high altitude. This is justified, as this group has contributed a great amount of knowledge to the field. On the other hand, just as a suggestion: There are other studies that have generated insight into cardiopulmonary pathophysiology of high altitude adaptation, especially the effects of high altitude on right-sided heart impairment (e.g. the summary of Sydykov A et al. Review Int J Environ Res Public Health 2021). It may be worthwhile mentioning and discussing the findings in these two distinct phenotypes of HF and bringing these findings into a more comprehensive context.

Thanks for the kind comment. As suggested, a brief paragraph about the effects of high altitude on right-sided heart impairment has been added.

- HF patients frequently ask whether it is safe to fly. Pressurized aircraft cabins operate at a barometric pressure that is comparable to an altitude of 1800-2500 m, depending on the aircraft type. It might be worthwhile and helpful for the readers to add a short comment/section on the common aspects of ascending to high altitude vs going on a commercial flight, and whether the findings from the mentioned hypoxia and high altitude studies may be transferred to air travel in HF or not. Absolutely agree. A very brief comment on this point has been added in the conclusions.

Minor Comments:

- Abstract: The conclusion that "HF patients should [...] undergo a specific "hypoxic-tailored

treatment" to avoid pharmacological interference with altitude adaptation mechanisms" should be reworded. It is well understood that this is a very promising option from a pathophysiological point of view, and that this option should be individually checked for HF patients. The authors have clearly pointed that out. However, the sentence in its current version may be erroneously suggesting a general recommendation of changing heart failure medication when going to higher altitude. You are right. The sentence has been changed to suggest that only beta-blocker therapy is worthy of modification in the case of high-altitude ascents.

- The introduction has a rather general character and is pretty long. It might be condensed. As suggested, the introduction has been shortened.
- P14, l53: What is the meaning of "paraphysiological" in this context? The term is indeed confusing. The sentence has been changed.

Exercise in Hypoxia: a model from laboratory to on field studies

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Abstract

Clinical outcome and quality of life of chronic heart failure (HF) patients have greatly improved over the last two decades. These results and the availability of modern lifts allow many cardiac patients to spend leisure time at altitude. HF per se doesn't impede a safe stay at altitude, but exercise at both simulated and real altitude is associated with a reduction in performance, which is inversely proportional to HF severity. For example, in normal subjects, the reduction in functional capacity is ~2% every 1000 m altitude increase, whereas it is 4% and 10% in HF patients with normal or slightly diminished exercise capacity and in HF patients with markedly diminished exercise capacity. Also the on-field experience with HF patients at altitude confirm safety and shows overall similar data to that reported at simulated altitude. Even "optimal" HF treatment in patients spending time at altitude or at hypoxic conditions is likely different from optimal treatment at sea level, particularly as regards β-blockers selectivity. Furthermore, high altitude, both simulated or on-field, represents a stimulating model of hypoxia in HF patients and healthy subjects.

Our data suggest that spending time at altitude (<3500 m) can be safe even for HF patients, provided that subjects are free of co-morbidities that may directly interfere with the adaptation to altitude and are stable. However, HF patients experience a reduction of exercise capacity directly proportional to HF severity and altitude. Finally, HF patients should be tested for functional capacity and undergo a specific "hypoxic-tailored treatment" to avoid pharmacological interference with altitude adaptation mechanisms, particularly with regard to the selectivity of beta-blockers.

Introduction

The Centro Cardiologico Monzino has a long tradition of scientific studies at high altitude, either simulated or real. At first, these experiences were motivated by the desire to retrace the footsteps of Guido Monzino, the mid-20th century mountaineer to whom a hut on the Mont Blanc massif is dedicated, and by the pleasure of fully experiencing the mountains. But very soon, the opportunity to better understand the physiological mechanisms underlying the adaptation of the human body to hypoxia have moved a lot of scientist to continue to go to the mountains for scientific purpose, namely understanding how the body, both in the short and long term, adapts to the scarcity of oxygen.

As altitude increases, the availability of oxygen in the air decreases and, as a compensation, the body increases cardiovascular and respiratory work. Moreover, at altitude, the body's ability to utilise oxygen is also limited. This condition generates significant cardiovascular changes, which in borderline situations can lead to an increased risk of heart attack, stroke and acute pulmonary oedema, particularly if people practise sport at altitude [1].

The mountain, with its reduction of oxygen pressure in the inhaled air, is a perfect model for understanding what happens in case of hypoxia a condition similar for some aspects to that the heart failure (HF) patient faces every day. For these reasons we studied subjects also during exercise, a condition more similar to daily life, in which the organism continuously perform tasks and it is not at rest in the bed.

We started by studying altitude by simulating it in the laboratory, then chasing the real thing around the world: at Everest base camp, then to Capanna Margherita (Monte Rosa), to the Andes, and finally to Punta Helbronner on Mont Blanc. We certainly did not tackle this climb alone, but with the scientific help of many experienced scientists and climbing companions.

Monzino studies on adaptation of chronic heart failure patient to simulated altitude

To evaluate HF patients adaptation at altitude under hypobaric hypoxic conditions, although more physiologically correct, implies not inconsiderable logistical difficulties. However, it is possible to recreate

simulated altitude conditions in the laboratory by having the subject breathe hypoxic mixtures with known concentrations of nitrogen and oxygen. This is referred as normobaric hypoxia. The following table gives the expected levels of O_2 partial pressure in inhaled air at different altitudes and the corresponding FiO_2 required to obtain them during simulated altitude tests:

Simulated altitude (meters)	PO_2 inhaled air (mmHg)	FiO_2 inhaled air (%)
0-100	160	˜21
1000	140	18.3
1500	130	16.9
2000	125	16.2
2500	117	15.4
3000	110	14.4

This approach is burdened by some methodological limitations (among others, the differences in the expected pathophysiological effects between hypobaric and normobaric hypoxia and the possibility of studying the behavior of the system only under conditions of "acute" hypoxia), but it is relatively simple, clinically safe, and easily repeatable.

Our laboratory has been particularly dedicated to studies using normobaric hypoxia in patients with chronic HF, mimicking an altitude up to 3000 meters. The great majority of studies, however, utilized a simulated altitude of 2000 meters. The choice was driven by the consideration that this is the altitude to which patients most frequently request to go and because the corresponding reduction in PAO_2 is roughly the same as that found during the most common air travel. In fact, the main objective of these studies was to provide the physician with objective elements to answer questions increasingly asked by patients, such as "Can I go to the mountains?" "Up to what altitude?" "What activities can I do if I spend a holiday period in the mountains?" "Can I take the airplane?".

An early pioneering study [2] sought to quantify the expected reduction in functional capacity of normal (n=14) or chronic HF (n=38) subjects, in clinically stable conditions and of varying severity, during acute exposure to different simulated altitudes up to 3000 meters (specifically sea level, 1000 meters, 1500 meters, 2000 meters and 3000 meters). Functional capacity was measured by recording O_2 consumption (VO_2) at the peak of a maximal effort performed at the different simulated altitude levels. Patients with HF were divided into severity classes based on the peak VO_2 value recorded during the exercise test conducted in normoxia (mild decompensation: VO_2peak>20, moderate decompensation: VO_2peak between 15 and 20, and severe decompensation: VO_2peak <15 ml/Kg/min). On average, it was observed that for every 1000 mt of elevation gain, functional capacity was reduced by ~2% in healthy subjects, 4% in subjects with mild/moderate decompensation, and ~11% in subjects with severe decompensation. Although the numerosity of the study was not high, it is interesting to note that no adverse events related to acute exposure to simulated altitude occurred, regardless of the severity of decompensation or the extent of hypoxia (Figure 1). Moreover, this finding was confirmed in subsequent studies in which patients performed maximal or constant load exercise tests while breathing 16% FiO2 mixtures[1, 2, 3, 4]. Overall, in fact, ergometric tests were performed in 154 patients with stable chronic HF of varying severity, but including patients with severe functional impairment, without detecting any significant adverse events. Thus, it can be said that acute exposure to moderate altitude is relatively safe in the patient with chronic HF in clinical stability, although some degree of reduction in exercise capacity must be expected, especially in the most severe patients.

A second study [3], evaluated the relationship between maximum exercise capacity and lung diffusion (measured as DLCO, i.e., pulmonary diffusion for carbon monoxide) in 40 patients with chronic HF and 40 healthy controls. Half of the participants performed assessments under hypoxic conditions with FiO_2 16% as well. The study showed a significant correlation between peakVO_2 and DLCO at rest in all patients, a correlation even stronger under hypoxic conditions. In addition, by measuring diffusion during a constant low workload exercise, it was observed that under this specific exercise load DLCO rises but the less the DLCO increase with exercise the worse the maximal exercise performance during hypoxia. All this demonstrates that proper functioning of the alveolus capillary membrane is critical to preserving the functional capacity of

the patient with HF and that this is even truer under conditions of reduced O_2 availability, as it happens at altitude.

Subsequent studies have finally investigated the relationship between altitude and drug therapy, with special reference to β-blockers, whose effects may be particularly affected, directly or reflexively, by hypoxia.

A study published in 2006 [4] evaluated the cardiorespiratory response to exercise under simulated altitude conditions (FiO_2 16%, simulated altitude 2000 mt) in 15 patients with chronic HF treated with placebo or carvedilol according to a cross-over design. All patients performed four cardiorespiratory exercise tests: a symptom limited maximal exercise test applying a ramp workload protocol and a constant low workload test both in normoxia and hypoxia. Whatever the condition evaluated, the ventilatory response to exercise appeared significantly reduced in carvedilol, both as an absolute value and relative to CO_2 produced (lower slope of the VE/VCO_2 relationship), with a significant increase in CO_2 tele-expiratory pressure in the intermediate phases of exercise, the latter finding suggesting an inhibitory influence of the βblocker on chemoreceptor sensitivity in HF patients. Beyond pathophysiological considerations, however, hemogasalytic blood samples taken during the steady state phase of the constant-load test showed, under hypoxic conditions, a significantly greater reduction in PaO_2 during carvedilol therapy than during placebo. This observation leads us to believe that while the containment of excessive ventilatory response to exercise by carvedilol is generally desirable in HF patient, this same effect turns out to be counterproductive under hypoxic conditions, when hyperventilation becomes an important compensation mechanism to hypoxemia.

Complementing these evaluations, a more recent study [5] investigated the cardiorespiratory response to exercise under normoxic and hypoxic conditions in 61 patients with HF by comparing the effects of treatment with different β-blockers characterized by different selectivity toward β1 and β2 receptors (nonselective Carvedilol and strongly β1 receptors selective βNebivolol, and Bisoprolol), once again using a cross-over design (patients alternately took the three drugs for a period of 2 months each). The study in hypoxia was performed by simulating an altitude of ~2000 mt (FiO_2 16%) at which the patient performed a constant-load cardiorespiratory exercise test at a workload equal to 50% of that reached at the peak of a maximal ramp

test. The same test was also performed under normoxic conditions. The study showed that the ventilatory response to exercise was lower in carvedilol, both under normoxic and hypoxic conditions, than in the other β-blockers, although no significant differences were found in the degree of induced hypoxemia. Inhibition of the ventilatory response to exercise by carvedilol proved to be related a chemoreceptorial interference. Indeed, chemoreceptor sensitivity, both central and peripheral, appeared significantly lower during treatment with carvedilol than with the other β-blockers. The study also showed, confirming data from a previous study [6], that treatment with carvedilol, unlike treatment with bisoprolol or nebivolol, interferes with the efficiency of gas exchange at the alveolus capillary membrane, as evidenced by the lower value of DLCO and of the membrane conductance subcomponent. Most likely, this effect can be traced directly to the blockade exerted by carvedilol on alveolar β2 receptors, whose role in maintaining alveolar fluid clearance is amply demonstrated. The interference of carvedilol with alveolar-capillary membrane efficiency constitutes a further disadvantage of this βblocker, compared with molecules with greater cardioselectivity, in the context of altitude adaptation.

Mount Everest South Base Camp (5400 m) - The HIGHCARE experience on the roof of the world.

The High Altitude Cardiovascular Research (HIGHCARE) study is a multidisciplinary Himalayan scientific expedition conducted in 2008 with the main objective of exploring the cardiovascular effects of high-altitude exposure in healthy subjects.

The destination of the expedition, led by Prof. Gianfranco Parati of the University of Milan Bicocca, which included 47 subjects who spent about three weeks exposed to high altitude, was Mount Everest South Base Camp. The camp is located at 5400 m a.s.l. in Nepal near the south face of Mount Everest, below the 'Ice Fall' glacier, and is reached after a 9-day hike. Here, cardiovascular and respiratory data were collected (both in the first 2 days of exposure and after 2 weeks spent at Base Camp) and then compared with data previously collected at sea level.

Monzino researchers demonstrated for the first time how exposure at high altitude is able to considerably increase lung diffusion capacity over time [7]. Specifically, they enrolled 33 healthy subjects (67% male,

40.8±10.4 years) and experimentally assessed their DLCO, both at sea level and after about 3 weeks at 5400 m. After this period of time, the haemoglobin oxygen saturation (SpO_2) increased from 77.2±6.0 to 85.3±3.6%. Compared to sea level, an increase was observed in haemoglobin (14.2±1.2 to 17.2±1.8 g/dl), DLCO (23.6±4.4 to 25.1±5.3 ml/min/mmHg), membrane diffusion and alveolar volume. Importantly, membrane diffusion normalised for alveolar volume also increased from 10.9±5.2 to 16.0±9.2 ml/min/mmHg/l. In addition, to demonstrating the feasibility of measuring DLCO at high-altitude, these data showed for the first time that the increase in DLCO is largely related to an increase of the membrane diffusion component. All these changes indicate a reduced resistance to the flow of gases through the alveolar-capillary membrane. The most likely mechanism seems to be the stimulation of Na^+-dependent receptors triggered by an increase in sympathetic impulse, often described at these altitudes.

Another study, led by prof Lombardi, focused on the incidence of periodic nocturnal breathing at altitude, with particular reference to gender differences [8]. The occurrence of altitude-induced sleep disturbances (particularly central apneas) is a frequent and well-documented phenomenon. However, for the first time, the authors demonstrated that central apneas are significantly more frequent among males than females. In this study, nocturnal cardiorespiratory monitoring was performed in 37 healthy subjects (23 males) at sea level, at 3400 m (Nanche Bazaar, during the first or second night spent at Mount Everest South Base Camp at 5400 m and after a 10-day stay at the camp. Despite the absence of documented pre-departure apnoeas at sea level, at 3400 m the apnoea-hypopnoea index values were 40.3±33 in males and 2.4±2.8 in females, thus highlighting the absence of a significant number of central apnoeas in females at this altitude. In contrast, at 5400 m, subjects of both sexes showed pathological values, although the magnitude was lower again in females (41.1±44.0 vs. 87.5±35.7). Interestingly, sleep disturbances tended to remain stable even after 10 days at base camp, suggesting that adaptation mechanisms may take longer for sleep parameters than for other respiratory parameters measured during wakefulness.

The authors also studied the role of continuous positive airway pressure (CPAP) treatment in improving SpO_2 values at high altitudes. This method, which is often used in emergencies to treat acute pulmonary oedema, consists in having the patient breathe under positive pressure. In the article by Agostoni et al. [9], they showed

that a 30-minute CPAP treatment in 16 healthy subjects after a 10-day stay at Mount Everest South Base Camp (5400 m) did not significantly improve SpO_2 (from 81 [78-85] to 80 [78-85]%). Furthermore, the authors compared the results obtained at Mount Everest South Base Camp with those obtained during another expedition to Capanna Regina Margherita hut (Monte Rosa, 4559 m). In the latter case, the same 30-minute CPAP treatment was applied to 23 healthy subjects, but strictly within 48 hours of acute altitude exposure, this time showing a significant improvement in SpO_2 parameters (from 80 [78-81] to 91 [84-97]%). These data demonstrate how the application of CPAP after short-term exposure to altitude is able to improve SpO_2, whereas this does not occur if subjects are exposed to high altitude for a prolonged time, despite the fact that pre-CPAP SpO_2 values were similar in both conditions. These results suggest that acutely some accumulation of fluid in the lungs is, at least in part, responsible for the low oxygen saturation of haemoglobin at high altitude, but that after prolonged exposure to high altitude there is no longer excess extravascular fluid present at the level of the alveoli-capillary membrane that can potentially be removed with CPAP. A possible practical implication of this study is that CPAP could be a useful manoeuvre for treating certain symptoms of altitude sickness related to low SpO_2 only during acute exposure to the hypobaric hypoxia typical of high altitude.

Apart from CPAP and sleep, at altitude SpO_2 and haemodynamics can be influenced simply by the subject's respiratory rate. In another interesting article, the HIGHCARE group, led by dr Bilo, demonstrated how changing one's breathing rhythm with deep, slow breathing significantly improves ventilation efficiency and O_2 parameters, as demonstrated by a significant increase in blood oxygenation [10]. Also, after 15 minutes of slow high tidal breathing (6 respiratory acts/minute), a reduction in systemic blood pressure and pulmonary pressure was observed, with no changes in DLCO. The study was conducted on healthy people living at sea level who stayed at 4559 m (Regina Margherita Hut, Monte Rosa) for 2-3 days (n=39) or at 5400 m (Mount Everest South Base Camp) for 12-16 days (n=28). The improvement in SpO_2 was most likely due to a reduction in dead space ventilation and an increase in alveolar ventilation, and was associated with a reduction in lung and systemic pressure levels, both of which were higher following exposure to high altitude (Figure 2).

Capanna Margherita - Experiments at Europe's highest mountain hut

The two expeditions to the Capanna Regina Margherita hut (4559 m) were conducted by the Centro Cardiologico Monzino and the Istituto Auxologico Italiano in 2008 and 2010, with the aim of deepening our knowledge of the effects of altitude on the body, both at rest and during exercise, and to evaluate the effect of certain drugs.

In both expeditions, the ascent took place over two days. On the first day, they climbed up to Alagna (1191 m) by car, continued by cable car to an altitude of 3200 m, and finally on foot to the Gnifetti refuge (3647 m), where they spent the night. The following morning, the ascent was continued on foot until reaching 4559 m, where all evaluations were carried out.

The article by Agostoni et al. [11] describes the results obtained on 8 healthy subjects who underwent a ramp cardiopulmonary testing at sea level (prior to departure) and at altitude, mainly with the aim of assessing changes in ventilation during exercise. The data, alongside a reduction in performance, show how the increase in ventilation triggered by hypoxia modifies the normal phases of exercise, anticipating the anaerobic threshold and causing the isocapnic buffering phase to disappear, or be reduced. This behaviour has been explained by hypothesising that the basal hyperventilation induced by acute exposure to hypoxia reduces CO_2 stores in the muscle, so that not enough remains to buffer the exercise-induced acidosis. This work about high-altitude physiology is also useful at sea level to understand why when we are a bit agitated our exercise capacity is reduced.

Another article [6]presented double-blind results on 27 subjects randomised to treatment for three weeks with β-blockers, carvedilol or nebivolol, compared with subjects in the placebo group. Again, subjects performed a cardiopulmonary ramp test at sea level before treatment, a second one after treatment, and finally a third test after at least two days of exposure to altitude. This study demonstrated different mechanisms of action of the two β-blockers, due to their different β-selectivity, showing that nebivolol has less impact on performance than carvedilol.

Alongside the line of research concerning exercise, another topic addressed by our protocols was the study of the underlying causes of the development of altitude sickness and of the possible drugs to counteract it. In a paper by Agostoni et al. [12], the effects on the alveolar-capillary membrane in 43 healthy subjects acutely exposed to high altitude are illustrated. The accumulation of fluid in the lungs, induced by exposure to a hypoxic environment, was found to be associated with a reduction in alveolar-capillary diffusion as early as the first day of stay at 4559 m and worsened further after the third day. Alongside this, however, a true breakdown of the alveolus-capillary barrier was not demonstrated, as assessed by Surfactant Binding Protein B (SPB) and Receptor for Advanced Glycation End-products (RAGE), two biomarkers associated precisely with lung damage.

Acetazolamide is a drug that is commonly used for the prevention and treatment of altitude sickness and now also in severe HF. For this reason, studies have been carried out at altitude randomising subjects to the use of this drug in order to study some as yet unknown aspects. A first study analysed how men show greater changes in breathing (periodic breathing) during sleep than women and how the use of acetazolamide has a positive effect by reducing apnoea and oxygenation in both sexes [13].

The effect of acetazolamide was also studied in another study by Salvi et al. [14], which evaluated the oxygen supply/demand ratio in the myocardium in 44 subjects randomised to treatment versus placebo. Analyses showed that while in patients treated with acetazolamide the reduction shown after exposure to high altitude returned to similar values compared to sea level in 3 days, subjects treated with placebo showed lower values. This study therefore laid the foundation for further investigations into the protective role of acetazolamide in coronary artery disease risk after exposure to high altitude.

Cardiopulmonary effects of acute high-altitude exposure: current results and future developments

Nowadays, the availability of modern ski-lifts guarantees the enjoyment of high altitude for every category of subject, from the healthy to the cardiopathic, from the young to the elderly.

The aim of the Monte Bianco-Skyway project, our most recent research on this topic, is to study the effects of acute exposure to high altitude on cardiorespiratory variables in a large, unselected population by helping to identify those most at risk.

In December 2019, a Keito K9 biometric station was installed and inaugurated at the mountain station of the Mont Blanc Cableways at Punta Helbronner, 3466 m. The instrument allows the measurement and collection of blood pressure, peripheral saturation, weight, height, age, lean and fat mass, drug therapy, smoking habits and comorbidities. This made it possible to obtain a 'snapshot' of the population approaching high altitudes for recreational reasons. The biometric station, which is multilingual and equipped with a touch screen, allows direct access to the data by the person concerned.

Between January and October 2020, 4874 volunteers (age 39.9±15.4, men 54.4%) underwent the assessment of their biometric parameters; of these, 3267 subjects provided all the required data. The mean peripheral saturation was 86.8±6.8%. On multivariate analysis, SpO_2 was significantly associated with age, sex, season, body mass index (BMI) and heart rate, but not with blood pressure. We identified 391 (12%) subjects with SpO_2 ≤80% (older, higher BMI and heart rate). These initial data show that high BMI values, older age and male gender are associated with an increased risk of hypoxia following exposure to high altitude, especially in winter [15].

Although slowed down by the COVID-19 pandemic, the pilot project continued with the placement, in August 2021, of a second fully automated biometric station located at the cable car departure point (1224 m). This will make it possible to better assess the effects of acute exposure to high altitude in terms of peripheral saturation, heart rate and pressure, comparing the values recorded upstream and downstream for each subject (Figure 3).

Thanks to the collection of anamnestic data (drug therapy, smoking habits and comorbidities), it will also be possible to 'phenotype' the population by stratifying it according to clinical history. In a second step, all recorded variables will be combined with the extent of reduction in oxygen saturation in order to construct

an easily calculable score indicative of each individual's specific risk of developing relevant disorders as a consequence of exposure to high altitude.

Hypoxia and right heart

Among the acute effects of acute exposure to hypoxia, pulmonary vasoconstriction resulting in the development of pulmonary hypertension assumes a major role, particularly in the development of high-altitude pulmonary edema (HAPE). While the mechanism of action still remains partly unknown, risk factors appear to be assisted fertilization birth, perinatal pulmonary hypertension, and advanced age, male sex, and rapid ascent. With prolonged exposure to the hypoxic stimulus, the development of pulmonary vessel remodeling, pulmonary hypertension with subsequent increase in right ventricular filling pressure leading to right heart failure can be observed (Int. J. Environ. Res. Public Health 2021, 18, 1692. https://doi.org/10.3390/ijerph18041692). Ref 16.

CONCLUSIONS

Simulated altitude studies conducted in our laboratory in HF patients reveal that acute exposure to moderate altitude (up to about 2000 m) is safe and well tolerated in subjects in stable clinical conditions, while little is known for altitudes above 3500m. Moreover, physical activity at altitude must not necessarily be prevented in these patients, but a reduction in functional capacity proportional to the severity of decompensation and the level of altitude achieved will have to be expected. In the light of these data, commercial airline flights, with cabin pressurisation equivalent to an altitude of 1800-2500m, also appear reasonably safe in this patient category.

Studies on the relationship between altitude and drug therapy have also shown that not all β-blockers can be used indifferently in patients with HF in whom frequent exposure to altitude can be expected. Indeed, in these conditions, cardio selective β-blockers, such as bisoprolol or nebivolol, appear to be preferable to nonselective β-blockers, such as carvedilol. Moreover, the study of both healthy people and patients at high altitude represents an extraordinary and stimulating model to evaluate pathological occupational and

recreational conditions characterized by hypoxia. Unfortunately, the available data come from small studies, making it expensive and complex to build prospective controlled studies.

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Figure legend:

Fig. 1 Mean reduction in maximum work rate with simulated altitude, as a percentage decrease from maximum work rate at 92 m. Slopes differed ($P < 0.05$) in healthy subjects filled squares) compared with patients, and between patients with normal (filled circles) or slightly diminished workload (filled triangles) compared with patients with markedly diminished workload (open circles).Reproduced from ref. [2].

Fig. 2 Scheme of the proposed timetable of lung fluid shift during high-altitude exposure. DLCO = lung diffusion for carbon monoxide, CPAP = continuous positive airway pressure, HbO2S = hemoglobin oxygen saturation. Reproduced from ref. [12]

Fig 3 Biometric multiparametric recording system (Keito K9; Keito, Barcelona, Spain) installed at Punta Helbronner (left) and at Entreves (right).

Exercise in Hypoxia: a model from laboratory to on field studies

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Abstract

Clinical outcome and quality of life of chronic heart failure (HF) patients have greatly improved over the last two decades. These results and the availability of modern lifts allow many cardiac patients to spend leisure time at altitude. HF per se doesn't impede a safe stay at altitude, but exercise at both simulated and real altitude is associated with a reduction in performance, which is inversely proportional to HF severity. For example, in normal subjects, the reduction in functional capacity is ~2% every 1000 m altitude increase, whereas it is 4% and 10% in HF patients with normal or slightly diminished exercise capacity and in HF patients with markedly diminished exercise capacity. Also the on-field experience with HF patients at altitude confirm safety and shows overall similar data to that reported at simulated altitude. Even "optimal" HF treatment in patients spending time at altitude or at hypoxic conditions is likely different from optimal treatment at sea level, particularly as regards β-blockers selectivity. Furthermore, high altitude, both simulated or on-field, represents a stimulating model of hypoxia in HF patients and healthy subjects.

Our data suggest that spending time at altitude (<3500 m) can be safe even for HF patients, provided that subjects are free of co-morbidities that may directly interfere with the adaptation to altitude and are stable. However, HF patients experience a reduction of exercise capacity directly proportional to HF severity and altitude. Finally, HF patients should be tested for functional capacity and undergo a specific "hypoxic-tailored treatment" to avoid pharmacological interference with altitude adaptation mechanisms, particularly with regard to the selectivity of beta-blockers.

Introduction

The Centro Cardiologico Monzino has a long tradition of scientific studies at high altitude, either simulated or real. At first, these experiences were motivated by the desire to retrace the footsteps of Guido Monzino, the mid-20th century mountaineer to whom a hut on the Mont Blanc massif is dedicated, and by the pleasure of fully experiencing the mountains~~, a magical place where hearing and sight become the main senses.~~. But very soon, the opportunity to better understand the physiological mechanisms underlying the adaptation of the human body to hypoxia have moved a lot of scientist to continue to go to the mountains for scientific purpose, namely understanding how the body, both in the short and long term, adapts to the scarcity of ~~the most precious commodity we have, so taken for granted at sea level: oxygen.~~oxygen.

As altitude increases, the availability of oxygen in the air decreases and, as a compensation, the body increases cardiovascular and respiratory work. Moreover, at altitude, the body's ability to utilise oxygen is also limited. ~~Thus, on the one hand, there is less oxygen available and, on the other, a lower capacity to utilise it.~~ This condition generates significant cardiovascular changes, which in borderline situations can lead to an increased risk of heart attack, stroke and acute pulmonary oedema~~. If~~, particularly if people practise sport at altitude~~, this risk is even greater because of the increased need for oxygen~~ [1].

The mountain, with its reduction of oxygen pressure in the inhaled air, is a perfect model for understanding what happens ~~when the air becomes thinner, even in the absence of heart, lung, kidney and muscle disease. Moreover, for those of us who deal with heart failure (HF), the high-altitude model represents an opportunity to study how the organism reacts~~ in case of hypoxia~~,~~ a condition similar for some aspects to that ~~that~~ the heart failure (HF) patient faces every day. For these reasons we ~~took the opportunity to study~~studied subjects ~~not only in a stationary position but~~ also ~~in a dynamic one~~during exercise, a condition more similar to daily life, in which the organism continuously perform tasks and it is not at rest in the bed.

We started by studying altitude by simulating it in the laboratory, then chasing the real thing around the world~~, with experiments conducted in often inaccessible locations where collecting accurate data becomes~~

~~complex, challenging but also very stimulating~~: at Everest base camp, then to Capanna Margherita (Monte Rosa), to the Andes, and finally to Punta Helbronner on Mont Blanc. We certainly did not tackle this climb alone, but with the scientific help of many experienced scientists and climbing companions.

Monzino studies on adaptation of chronic heart failure patient to simulated altitude

To evaluate HF patients adaptation at altitude under hypobaric hypoxic conditions, although more physiologically correct, implies not inconsiderable logistical difficulties. However, it is possible to recreate simulated altitude conditions in the laboratory by having the subject breathe hypoxic mixtures with known concentrations of nitrogen and oxygen. This is referred as normobaric hypoxia. The following table gives the expected levels of O_2 partial pressure in inhaled air at different altitudes and the corresponding FiO_2 required to obtain them during simulated altitude tests:

Simulated altitude (meters)	PO_2 inhaled air (mmHg)	FiO_2 inhaled air (%)
0-100	160	~21
1000	140	18.3
1500	130	16.9
2000	125	16.2
2500	117	15.4
3000	110	14.4

This approach is burdened by some methodological limitations (among others, the differences in the expected pathophysiological effects between hypobaric and normobaric hypoxia and the possibility of studying the behavior of the system only under conditions of "acute" hypoxia), but it is relatively simple, clinically safe, and easily repeatable.

Our laboratory has been particularly dedicated to studies using normobaric hypoxia in patients with chronic HF, mimicking an altitude up to 3000 meters. The great majority of studies, however, utilized a simulated altitude of 2000 meters. The choice was driven by the consideration that this is the altitude to which patients

most frequently request to go and because the corresponding reduction in PAO_2 is roughly the same as that found during the most common air travel. In fact, the main objective of these studies was to provide the physician with objective elements to answer questions increasingly asked by patients, such as "Can I go to the mountains?" "Up to what altitude?" "What activities can I do if I spend a holiday period in the mountains?" "Can I take the airplane?".

An early pioneering study [2] sought to quantify the expected reduction in functional capacity of normal (n=14) or chronic HF (n=38) subjects, in clinically stable conditions and of varying severity, during acute exposure to different simulated altitudes up to 3000 meters (specifically sea level, 1000 meters, 1500 meters, 2000 meters and 3000 meters). Functional capacity was measured by recording O_2 consumption (VO_2) at the peak of a maximal effort performed at the different simulated altitude levels. Patients with HF were divided into severity classes based on the peak VO_2 value recorded during the exercise test conducted in normoxia (mild decompensation: VO_2peak>20, moderate decompensation: VO_2peak between 15 and 20, and severe decompensation: VO_2peak <15 ml/Kg/min). On average, it was observed that for every 1000 mt of elevation gain, functional capacity was reduced by ~2% in healthy subjects, 4% in subjects with mild/moderate decompensation, and ~11% in subjects with severe decompensation. Although the numerosity of the study was not high, it is interesting to note that no adverse events related to acute exposure to simulated altitude occurred, regardless of the severity of decompensation or the extent of hypoxia (Figure 1). Moreover, this finding was confirmed in subsequent studies in which patients performed maximal or constant load exercise tests while breathing 16% FiO2 mixtures[1, 2, 3, 4]. Overall, in fact, ergometric tests were performed in 154 patients with stable chronic HF of varying severity, but including patients with severe functional impairment, without detecting any significant adverse events. Thus, it can be said that acute exposure to moderate altitude is relatively safe in the patient with chronic HF in clinical stability, although some degree of reduction in exercise capacity must be expected, especially in the most severe patients.

A second study [3], evaluated the relationship between maximum exercise capacity and lung diffusion (measured as DLCO, i.e., pulmonary diffusion for carbon monoxide) in 40 patients with chronic HF and 40

healthy controls. Half of the participants performed assessments under hypoxic conditions with FiO_2 16% as well. The study showed a significant correlation between peakVO_2 and DLCO at rest in all patients, a correlation even stronger under hypoxic conditions. In addition, by measuring diffusion during a constant low workload exercise, it was observed that under this specific exercise load DLCO rises but the less the DLCO increase with exercise the worse the maximal exercise performance during hypoxia. All this demonstrates that proper functioning of the alveolus capillary membrane is critical to preserving the functional capacity of the patient with HF and that this is even truer under conditions of reduced O_2 availability, as it happens at altitude.

Subsequent studies have finally investigated the relationship between altitude and drug therapy, with special reference to β-blockers, whose effects may be particularly affected, directly or reflexively, by hypoxia.

A study published in 2006 [4] evaluated the cardiorespiratory response to exercise under simulated altitude conditions (FiO_2 16%, simulated altitude 2000 mt) in 15 patients with chronic HF treated with placebo or carvedilol according to a cross-over design. All patients performed four cardiorespiratory exercise tests: a symptom limited maximal exercise test applying a ramp workload protocol and a constant low workload test both in normoxia and hypoxia. Whatever the condition evaluated, the ventilatory response to exercise appeared significantly reduced in carvedilol, both as an absolute value and relative to CO_2 produced (lower slope of the VE/VCO_2 relationship), with a significant increase in CO_2 tele-expiratory pressure in the intermediate phases of exercise, the latter finding suggesting an inhibitory influence of the βblocker on chemoreceptor sensitivity in HF patients. Beyond pathophysiological considerations, however, hemogasalytic blood samples taken during the steady state phase of the constant-load test showed, under hypoxic conditions, a significantly greater reduction in PaO_2 during carvedilol therapy than during placebo. This observation leads us to believe that while the containment of excessive ventilatory response to exercise by carvedilol is generally desirable in HF patient, this same effect turns out to be counterproductive under hypoxic conditions, when hyperventilation becomes an important compensation mechanism to hypoxemia.

Complementing these evaluations, a more recent study [5] investigated the cardiorespiratory response to exercise under normoxic and hypoxic conditions in 61 patients with HF by comparing the effects of treatment with different β-blockers characterized by different selectivity toward β1 and β2 receptors (nonselective Carvedilol and strongly β1 receptors selective βNebivolol, and Bisoprolol), once again using a cross-over design (patients alternately took the three drugs for a period of 2 months each). The study in hypoxia was performed by simulating an altitude of ~2000 mt (FiO_2 16%) at which the patient performed a constant-load cardiorespiratory exercise test at a workload equal to 50% of that reached at the peak of a maximal ramp test. The same test was also performed under normoxic conditions. The study showed that the ventilatory response to exercise was lower in carvedilol, both under normoxic and hypoxic conditions, than in the other β-blockers, although no significant differences were found in the degree of induced hypoxemia. Inhibition of the ventilatory response to exercise by carvedilol proved to be related a chemoreceptorial interference. Indeed, chemoreceptor sensitivity, both central and peripheral, appeared significantly lower during treatment with carvedilol than with the other β-blockers. The study also showed, confirming data from a previous study [6], that treatment with carvedilol, unlike treatment with bisoprolol or nebivolol, interferes with the efficiency of gas exchange at the alveolus capillary membrane, as evidenced by the lower value of DLCO and of the membrane conductance subcomponent. Most likely, this effect can be traced directly to the blockade exerted by carvedilol on alveolar β2 receptors, whose role in maintaining alveolar fluid clearance is amply demonstrated. The interference of carvedilol with alveolar-capillary membrane efficiency constitutes a further disadvantage of this βblocker, compared with molecules with greater cardioselectivity, in the context of altitude adaptation.

Mount Everest South Base Camp (5400 m) - The HIGHCARE experience on the roof of the world.

The High Altitude Cardiovascular Research (HIGHCARE) study is a multidisciplinary Himalayan scientific expedition conducted in 2008 with the main objective of exploring the cardiovascular effects of high-altitude exposure in healthy subjects.

The destination of the expedition, led by Prof. Gianfranco Parati of the University of Milan Bicocca, which included 47 subjects who spent about three weeks exposed to high altitude, was Mount Everest South Base Camp. The camp is located at 5400 m a.s.l. in Nepal near the south face of Mount Everest, below the 'Ice Fall' glacier, and is reached after a 9-day hike. Here, cardiovascular and respiratory data were collected (both in the first 2 days of exposure and after 2 weeks spent at Base Camp) and then compared with data previously collected at sea level.

Monzino researchers demonstrated for the first time how exposure at high altitude is able to considerably increase lung diffusion capacity over time [7]. Specifically, they enrolled 33 healthy subjects (67% male, 40.8±10.4 years) and experimentally assessed their DLCO, both at sea level and after about 3 weeks at 5400 m. After this period of time, the haemoglobin oxygen saturation (SpO_2) increased from 77.2±6.0 to 85.3±3.6%. Compared to sea level, an increase was observed in haemoglobin (14.2±1.2 to 17.2±1.8 g/dl), DLCO (23.6±4.4 to 25.1±5.3 ml/min/mmHg), membrane diffusion and alveolar volume. Importantly, membrane diffusion normalised for alveolar volume also increased from 10.9±5.2 to 16.0±9.2 ml/min/mmHg/l. In addition, to demonstrating the feasibility of measuring DLCO at high-altitude, these data showed for the first time that the increase in DLCO is largely related to an increase of the membrane diffusion component. All these changes indicate a reduced resistance to the flow of gases through the alveolar-capillary membrane. The most likely mechanism seems to be the stimulation of Na^+-dependent receptors triggered by an increase in sympathetic impulse, often described at these altitudes.

Another study, led by prof Lombardi, focused on the incidence of periodic nocturnal breathing at altitude, with particular reference to gender differences [8]. The occurrence of altitude-induced sleep disturbances (particularly central apneas) is a frequent and well-documented phenomenon. However, for the first time, the authors demonstrated that central apneas are significantly more frequent among males than females. In this study, nocturnal cardiorespiratory monitoring was performed in 37 healthy subjects (23 males) at sea level, at 3400 m (Nanche Bazaar, during the first or second night spent at Mount Everest South Base Camp at 5400 m and after a 10-day stay at the camp. Despite the absence of documented pre-departure apnoeas at sea level, at 3400 m the apnoea-hypopnoea index values were 40.3±33 in males and 2.4±2.8 in females,

thus highlighting the absence of a significant number of central apnoeas in females at this altitude. In contrast, at 5400 m, subjects of both sexes showed pathological values, although the magnitude was lower again in females (41.1±44.0 vs. 87.5±35.7). Interestingly, sleep disturbances tended to remain stable even after 10 days at base camp, suggesting that adaptation mechanisms may take longer for sleep parameters than for other respiratory parameters measured during wakefulness.

The authors also studied the role of continuous positive airway pressure (CPAP) treatment in improving SpO_2 values at high altitudes. This method, which is often used in emergencies to treat acute pulmonary oedema, consists in having the patient breathe under positive pressure. In the article by Agostoni et al. [9], they showed that a 30-minute CPAP treatment in 16 healthy subjects after a 10-day stay at Mount Everest South Base Camp (5400 m) did not significantly improve SpO_2 (from 81 [78-85] to 80 [78-85]%). Furthermore, the authors compared the results obtained at Mount Everest South Base Camp with those obtained during another expedition to Capanna Regina Margherita hut (Monte Rosa, 4559 m). In the latter case, the same 30-minute CPAP treatment was applied to 23 healthy subjects, but strictly within 48 hours of acute altitude exposure, this time showing a significant improvement in SpO_2 parameters (from 80 [78-81] to 91 [84-97]%). These data demonstrate how the application of CPAP after short-term exposure to altitude is able to improve SpO_2, whereas this does not occur if subjects are exposed to high altitude for a prolonged time, despite the fact that pre-CPAP SpO_2 values were similar in both conditions. These results suggest that acutely some accumulation of fluid in the lungs is, at least in part, responsible for the low oxygen saturation of haemoglobin at high altitude, but that after prolonged exposure to high altitude there is no longer excess extravascular fluid present at the level of the alveoli-capillary membrane that can potentially be removed with CPAP. A possible practical implication of this study is that CPAP could be a useful manoeuvre for treating certain symptoms of altitude sickness related to low SpO_2 only during acute exposure to the hypobaric hypoxia typical of high altitude.

Apart from CPAP and sleep, at altitude SpO_2 and haemodynamics can be influenced simply by the subject's respiratory rate. In another interesting article, the HIGHCARE group, led by dr Bilo, demonstrated how changing one's breathing rhythm with deep, slow breathing significantly improves ventilation efficiency and

O_2 parameters, as demonstrated by a significant increase in blood oxygenation [10]. Also, after 15 minutes of slow high tidal breathing (6 respiratory acts/minute), a reduction in systemic blood pressure and pulmonary pressure was observed, with no changes in DLCO. The study was conducted on healthy people living at sea level who stayed at 4559 m (Regina Margherita Hut, Monte Rosa) for 2-3 days (n=39) or at 5400 m (Mount Everest South Base Camp) for 12-16 days (n=28). The improvement in SpO_2 was most likely due to a reduction in dead space ventilation and an increase in alveolar ventilation, and was associated with a reduction in lung and systemic pressure levels, both of which were higher following exposure to high altitude (Figure 2).

Capanna Margherita - Experiments at Europe's highest mountain hut

The two expeditions to the Capanna Regina Margherita hut (4559 m) were conducted by the Centro Cardiologico Monzino and the Istituto Auxologico Italiano in 2008 and 2010, with the aim of deepening our knowledge of the effects of altitude on the body, both at rest and during exercise, and to evaluate the effect of certain drugs.

In both expeditions, the ascent took place over two days. On the first day, they climbed up to Alagna (1191 m) by car, continued by cable car to an altitude of 3200 m, and finally on foot to the Gnifetti refuge (3647 m), where they spent the night. The following morning, the ascent was continued on foot until reaching 4559 m, where all evaluations were carried out.

The article by Agostoni et al. [11] describes the results obtained on 8 healthy subjects who underwent a ramp cardiopulmonary testing at sea level (prior to departure) and at altitude, mainly with the aim of assessing changes in ventilation during exercise. The data, alongside a reduction in performance, show how the increase in ventilation triggered by hypoxia modifies the normal phases of exercise, anticipating the anaerobic threshold and causing the isocapnic buffering phase to disappear, or be reduced. This behaviour has been explained by hypothesising that the basal hyperventilation induced by acute exposure to hypoxia reduces CO_2 stores in the muscle, so that not enough remains to buffer the exercise-induced acidosis. This

work about high-altitude physiology is also useful at sea level to understand why when we are a bit agitated our exercise capacity is reduced.

Another article [6]presented double-blind results on 27 subjects randomised to treatment for three weeks with β-blockers, carvedilol or nebivolol, compared with subjects in the placebo group. Again, subjects performed a cardiopulmonary ramp test at sea level before treatment, a second one after treatment, and finally a third test after at least two days of exposure to altitude. This study demonstrated different mechanisms of action of the two β-blockers, due to their different β-selectivity, showing that nebivolol has less impact on performance than carvedilol.

Alongside the line of research concerning exercise, another topic addressed by our protocols was the study of the underlying causes of the development of altitude sickness and of the possible drugs to counteract it. In a paper by Agostoni et al. [12], the effects on the alveolar-capillary membrane in 43 healthy subjects acutely exposed to high altitude are illustrated. The accumulation of fluid in the lungs, induced by exposure to a hypoxic environment, was found to be associated with a reduction in alveolar-capillary diffusion as early as the first day of stay at 4559 m and worsened further after the third day. Alongside this, however, a true breakdown of the alveolus-capillary barrier was not demonstrated, as assessed by Surfactant Binding Protein B (SPB) and Receptor for Advanced Glycation End-products (RAGE), two biomarkers associated precisely with lung damage.

Acetazolamide is a drug that is commonly used for the prevention and treatment of altitude sickness and now also in severe HF. For this reason, studies have been carried out at altitude randomising subjects to the use of this drug in order to study some as yet unknown aspects. A first study analysed how men show greater changes in breathing (periodic breathing) during sleep than women and how the use of acetazolamide has a positive effect by reducing apnoea and oxygenation in both sexes [13].

The effect of acetazolamide was also studied in another study by Salvi et al. [14], which evaluated the oxygen supply/demand ratio in the myocardium in 44 subjects randomised to treatment versus placebo. Analyses showed that while in patients treated with acetazolamide the reduction shown after exposure to high

altitude returned to similar values compared to sea level in 3 days, subjects treated with placebo showed lower values. This study therefore laid the foundation for further investigations into the protective role of acetazolamide in coronary artery disease risk after exposure to high altitude.

Cardiopulmonary effects of acute high-altitude exposure: current results and future developments

Nowadays, the availability of modern ski-lifts guarantees the enjoyment of high altitude for every category of subject, from the healthy to the cardiopathic, from the young to the elderly.

The aim of the Monte Bianco-Skyway project, our most recent research on this topic, is to study the effects of acute exposure to high altitude on cardiorespiratory variables in a large, unselected population by helping to identify those most at risk.

In December 2019, a Keito K9 biometric station was installed and inaugurated at the mountain station of the Mont Blanc Cableways at Punta Helbronner, 3466 m. The instrument allows the measurement and collection of blood pressure, peripheral saturation, weight, height, age, lean and fat mass, drug therapy, smoking habits and comorbidities. This made it possible to obtain a 'snapshot' of the population approaching high altitudes for recreational reasons. The biometric station, which is multilingual and equipped with a touch screen, allows direct access to the data by the person concerned.

Between January and October 2020, 4874 volunteers (age 39.9±15.4, men 54.4%) underwent the assessment of their biometric parameters; of these, 3267 subjects provided all the required data. The mean peripheral saturation was 86.8±6.8%. On multivariate analysis, SpO_2 was significantly associated with age, sex, season, body mass index (BMI) and heart rate, but not with blood pressure. We identified 391 (12%) subjects with SpO_2 ≤80% (older, higher BMI and heart rate). These initial data show that high BMI values, older age and male gender are associated with an increased risk of hypoxia following exposure to high altitude, especially in winter [15].

Although slowed down by the COVID-19 pandemic, the pilot project continued with the placement, in August 2021, of a second fully automated biometric station located at the cable car departure point (1224 m). This will make it possible to better assess the effects of acute exposure to high altitude in terms of peripheral saturation, heart rate and pressure, comparing the values recorded upstream and downstream for each subject (Figure 3).

Thanks to the collection of anamnestic data (drug therapy, smoking habits and comorbidities), it will also be possible to 'phenotype' the population by stratifying it according to clinical history. In a second step, all recorded variables will be combined with the extent of reduction in oxygen saturation in order to construct an easily calculable score indicative of each individual's specific risk of developing relevant disorders as a consequence of exposure to high altitude.

Hypoxia and right heart

Among the acute effects of acute exposure to hypoxia, pulmonary vasoconstriction resulting in the development of pulmonary hypertension assumes a major role, particularly in the development of high-altitude pulmonary edema (HAPE). While the mechanism of action still remains partly unknown, risk factors appear to be assisted fertilization birth, perinatal pulmonary hypertension, and advanced age, male sex, and rapid ascent. With prolonged exposure to the hypoxic stimulus, the development of pulmonary vessel remodeling, pulmonary hypertension with subsequent increase in right ventricular filling pressure leading to right heart failure can be observed (Int. J. Environ. Res. Public Health 2021, 18, 1692. https://doi.org/10.3390/ijerph18041692). Ref 16.

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CONCLUSIONS

Simulated altitude studies conducted in our laboratory in HF patients reveal that acute exposure to moderate altitude (up to about 2000 m) is safe and well tolerated in subjects in stable clinical conditions, while little is known for altitudes above 3500m. Moreover, physical activity at altitude must not necessarily be prevented in these patients, but a reduction in functional capacity proportional to the severity of

decompensation and the level of altitude achieved will have to be expected. In the light of these data, commercial airline flights, with cabin pressurisation equivalent to an altitude of 1800-2500m, also appear reasonably safe in this patient category.

Studies on the relationship between altitude and drug therapy have also shown that not all β-blockers can be used indifferently in patients with HF in whom frequent exposure to altitude can be expected. Indeed, in these conditions, cardio selective β-blockers, such as bisoprolol or nebivolol, appear to be preferable to nonselective β-blockers, such as carvedilol. Moreover, the study of both healthy people and patients at high altitude represents an extraordinary and stimulating model to evaluate pathological occupational and ~~paraphysiological~~recreational conditions characterized by hypoxia. Unfortunately, the available data come from small studies, making it expensive and complex to build prospective controlled studies.

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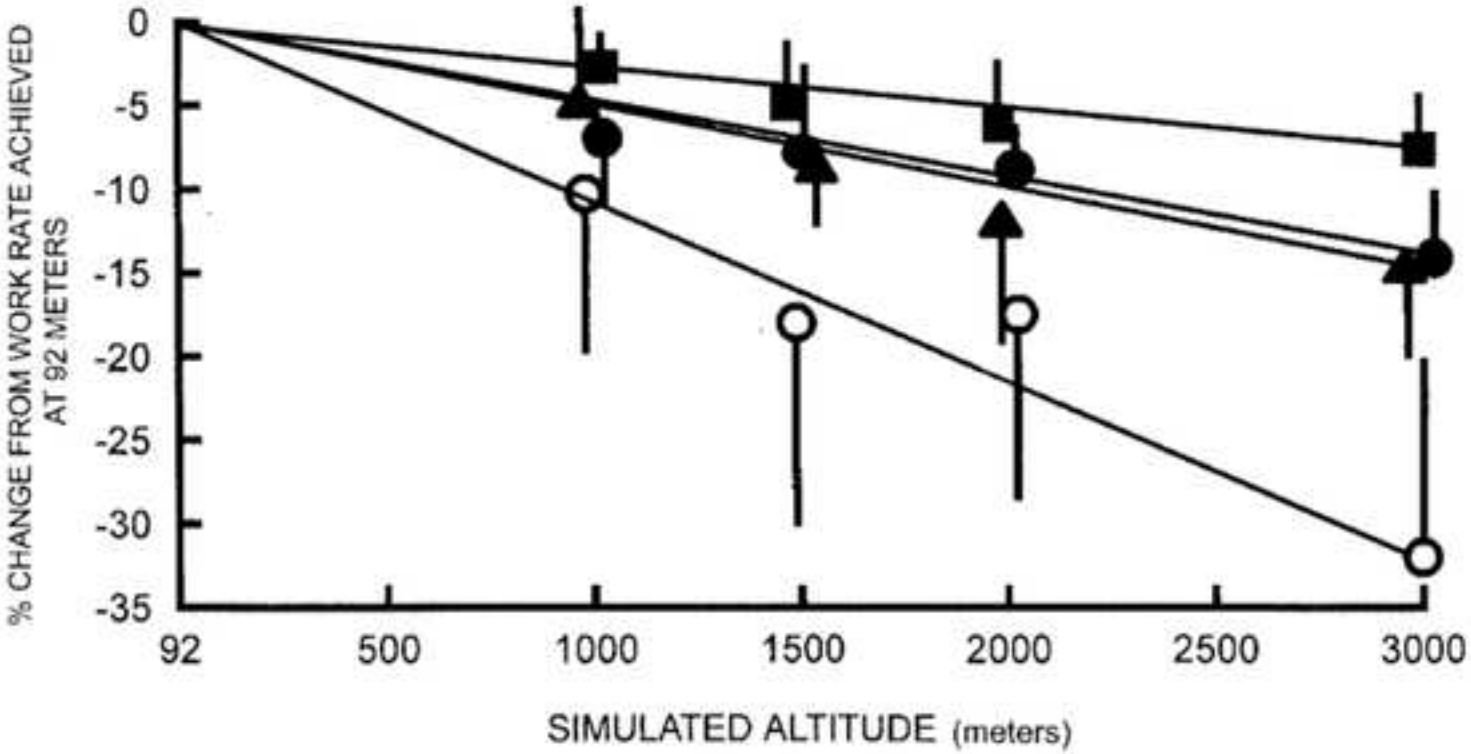
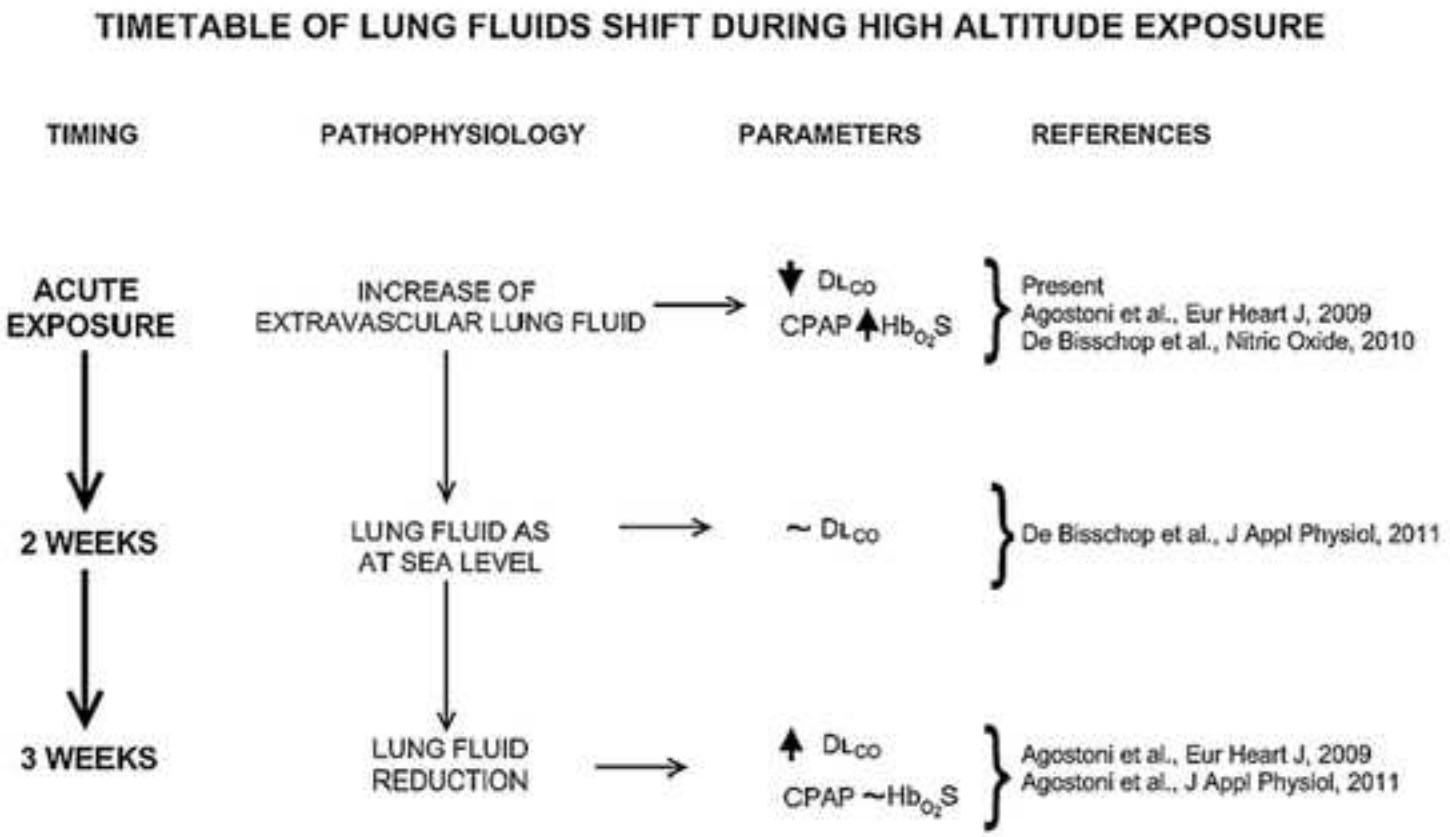
Figure legend:

Fig. 1 Mean reduction in maximum work rate with simulated altitude, as a percentage decrease from maximum work rate at 92 m. Slopes differed ($P < 0.05$) in healthy subjects filled squares) compared with patients, and between patients with normal (filled circles) or slightly diminished workload (filled triangles) compared with patients with markedly diminished workload (open circles).Reproduced from ref. [2].

Fig. 2 Scheme of the proposed timetable of lung fluid shift during high-altitude exposure. DLCO = lung diffusion for carbon monoxide, CPAP = continuous positive airway pressure, HbO2S = hemoglobin oxygen saturation. Reproduced from ref. [12]

Fig 3 Biometric multiparametric recording system (Keito K9; Keito, Barcelona, Spain) installed at Punta Helbronner (left) and at Entreves (right).





Hypoxia and HF

COMMERCIAL FLIGHTS

MOUNTAIN ASCENTS (BY LIFT AND/OR FOOT)

HIGH ALTITUDE WORKING ACTIVITIES

- Evaluation of comorbidities
- Evaluation of HF drugs
- Exercise capacity evaluation (CPET) and lung diffusion (DLCO/DLNO)

- Slow ascent (300-500m /day if above 2500m)
- NYHA I-II. No more than 3500m, no more than moderate physical activity
- NYHA II. No more than 3000m, no more than light physical activity
- Unstable/NYHA IV: avoid hypoxic conditions