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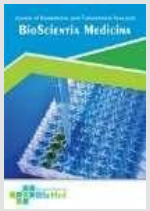

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High Altitude Pulmonary Physiology

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A B S T R A C T

High altitude is defined as regions above 2400 meters above sea level. Almost 2% of the world's population dwells in high-altitude regions of the world. The respiratory system plays an important role in determining survival and undergoes a series of adaptive changes to compensate for hypobaric hypoxic states (decreased barometric pressure with increasing altitude) including increased alveolar ventilation, diffusion capacity, pulmonary vascular vasoconstriction, increased cardiac output, shifted of oxyhemoglobin dissociation curve and polycythemia. Being at a high altitude suddenly without compensation can be bad and cause medical problems that will arise when at an altitude due to a decrease in PaO2 caused by a drop in barometric pressure.

1. Introduction

The geographical conditions of the world consist of highlands and lowlands. Highlands are areas that are above 2400 meters above sea level, and lowlands are areas that are at 350 meters above sea level.[1] Likewise, geographically, Indonesia is a country located on the Ring of Fire, where there are many volcanoes scattered throughout Indonesia. Overall, Indonesia has 129 volcanoes and has many highlands and lowlands that are evenly distributed.[2]

The percentage of the human population living in the highlands, which is almost 2% of the world's population, or more than 140 million people, lives at an altitude above 1500 meters above sea level, while it is estimated that as many as 40 million people travel to the highlands or the life temporarily. Some activities such as for relaxing, exercising, adventuring, doing mining activities, scientific research, and for many other reasons, including religion.[3]

The barometric pressure at sea level is 760 mmHg with a partial pressure of oxygen around 159 mmHg (fiO_2 21%) at sea level, while at the top of Mount Everest (88,848 meters), the barometric pressure is 253 mmHg with a partial pressure of oxygen of 53 mmHg. This condition, known as hypobaric hypoxia, is caused by a decrease in barometric pressure with increasing altitude.[4] The respiratory system plays a significant role in determining survival and undergoes a series of adaptive changes to compensate for hypobaric hypoxia and optimize oxygen transport and utilization to tissues.[5]

Research conducted by Taufik et al. on residents living in the village of Girian Bitung and the village of

Wulurmartus South Minahasa (1080 meters) found that the oxygen saturation of the population in the highlands was lower than in the lowlands. Similar results were obtained by Beall et al., who investigated different forms of biological adaptation in the Andean (4000m), Tibean (5000m), and Ethiopia (3530m). Beall et al. reported that there was a decrease in oxygen saturation, an increase in hemoglobin levels, and a decrease in oxygen partial pressure when at high altitudes.[6,7] Research conducted by Gassmann et al. found that the inhabitants of the Andean highlands showed a much more significant increase in Hb compared to all other populations in the world.[8]

In addition, hypoxia also increases pulmonary ventilation and cardiac output and increases erythrocyte production to compensate for the decrease in barometric pressure. The effect of this hypoxic hypobaric state causes a variety of conditions that can be life-threatening. In some cases, those who cannot tolerate and adapt to low oxygen levels will produce a maladaptive response in the form of high-altitude illness. The prevalence of this case varies between 40-90% depending on the altitude and susceptibility of individuals who are not acclimatized and continue to climb more than 500 meters to an altitude of 4500-6000 meters, while passive climbing 3000-3500 meters has a prevalence of 25-40%.[9]

Lung physiology at altitude

Respiration or breathing is the body's effort to meet the needs of O_2 in the metabolic process and expel CO_2 as a result of metabolism through the intermediary organs of the lungs and respiratory tract together with the cardiovascular system so that oxygen-rich blood is produced. Respiration has 3 stages: ventilation, diffusion, and perfusion. These three components always work together, and if there is a disturbance in one or more components, there will be gas exchange disturbances. A person's lung function situation is said to be normal if the results of the work of ventilation, diffusion, perfusion, and the relationship between ventilation and perfusion produce normal arterial blood gas partial pressures (PaO_2 and $PaCO_2$).[10]

Geographical aspects

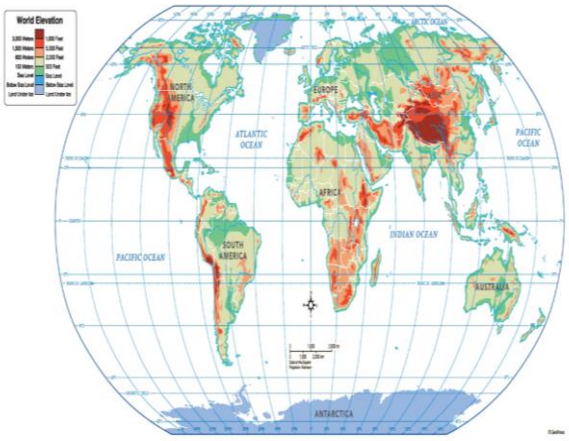

Figure 1. Highlands in the world

Highlands are defined as areas above 2400 meters above sea level (8000 feet). The region is further subdivided into very highlands – 3500 meters to 5500 meters (11,500 – 18,000 ft) and extreme highlands – more than 5500 meters (>18,000 ft).[11,12]

Table 1. Altitude, barometric pressure, and partial pressure of inspired oxygen

Altitude (meters)	Altitude (feet)	Barometric pressure (mmHg)	PO_2 (mmHg)
0	0	760	159
1000	3280	674	141
2000	6560	596	125
3000	9840	526	110
4000	13,120	463	97
5000	16,400	405	85
6000	19,680	354	79
8000	26,240	268	56
88848	29,028	253	43

A decrease in the partial pressure of oxygen in the air causes a lower partial pressure of oxygen (PO_2) at each stage in the oxygen transport chain as oxygen moves from the atmosphere to the tissues causing decreased availability of oxygen for phosphorylation in the mitochondria of cells. Oxygen cascade both at sea level and at high altitude is depicted in Figure 1.[13]

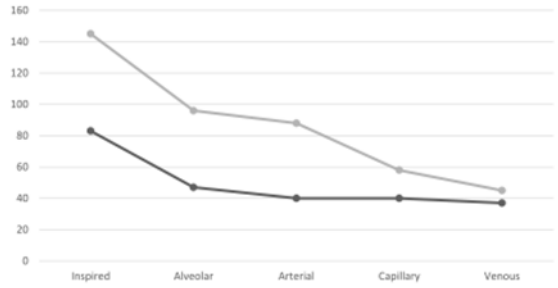

Figure 2. Oxygen cascade both at sea level and at 4450 meters

Adaptation of the respiratory system at highlands

Adaptation in various stages of oxygen transfer to overcome tissue hypoxia as a result of oxygen availability less for metabolism, blood oxygenation, and cellular oxidative phosphorylation. These adaptations are complementary and can be acute (immediately up to 5 days), subacute (over a few weeks), chronic (several months to several years), or lifelong, depending on the duration of exposure to the highlands.[12,14]

Ventilation response

In acute response to hypoxia, alveolar ventilation will increase. Ventilatory response to hypoxia (HVR) causes a decrease in alveolar PCO_2 to compensate for the lower partial pressure of oxygen in the blood (PaO_2). The large increase in ventilation generally cannot be seen until the $PaO2_A$falls. Below 60 mmHg and at any altitude, ventilation will continue to increase over a period of weeks. This process is called the acclimatization of ventilation data obtained from several individuals on the summit of Mount Everest (8400 m, barometric pressure 272 mmHg) with a $PaCO_2$ of 13 mmHg. As a result, because the inspired oxygen pressure was only 47 mmHg, the mean PaO_2 was 30 mmHg maintained. The ventilatory response to a hypoxic HVR is triggered by peripheral chemoreceptors in the carotid body. [14,15]

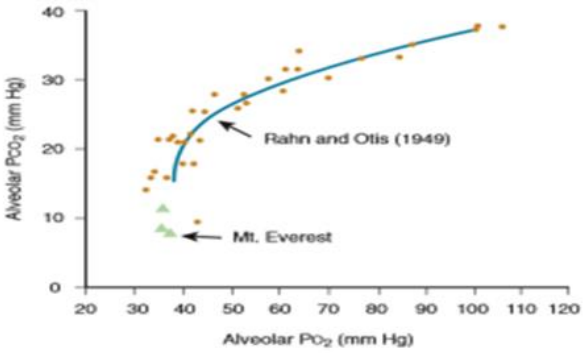

Figure 3. Oxygen–carbon dioxide diagram showing alveolar gas composition in acclimatized individuals

Hyperventilation persists over a period of several weeks and tends to return to normal after a few weeks at lower altitudes. During days to weeks at high altitudes, oxygen saturation improves as continued hyperventilation is maintained after the initial sudden drop in acute high-altitude exposure. Respiratory patterns change at high altitudes because of the response of central and peripheral chemoreceptors to dynamic changes and patterns of oscillation of oxygen and carbon dioxide levels in the blood. Hyperventilation causes carbon dioxide *to wash out* due to attacks of apnea because the PCO_2 falls below the threshold required to trigger central chemoreceptors. Periodic breathing with recurrent episodes of apnea and recurrent hyperpnea is a feature exhibited by a healthy person at high altitudes, appearing at moderate elevations as high as 2500 meters both during the wakefulness stage and at various stages of sleep. At extremely high altitudes above 5500 meters, periodic breathing disappears due to the high respiratory rate.[3,16]

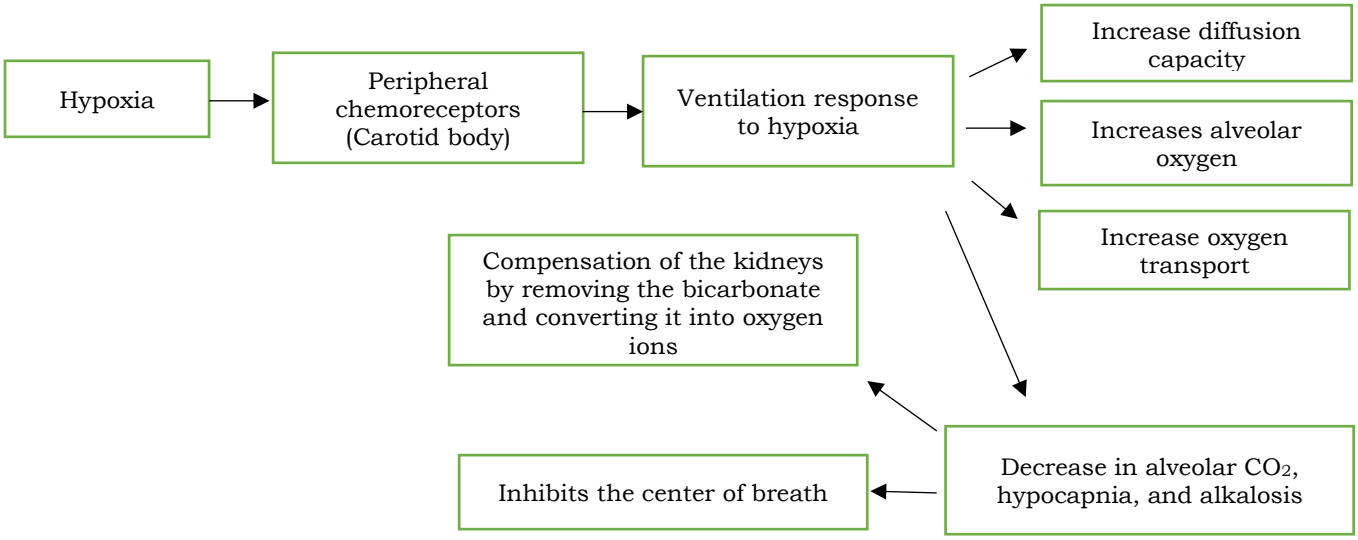

Figure 4. Response to hypoxia through the peripheral chemoreceptor system.

Lowland residents exposed to highlands have lower vital capacities due to changes in lung mechanics due to hypoxia and hypocapnia. There is airway narrowing, increased interstitial fluid, hypoxic pulmonary vasoconstriction, VQ mismatch, and decreased muscle strength. On the other hand, the highlanders had lower ventilation per minute than the lowlanders who were at the highlands under the same atmospheric

conditions due to carotid body hypertrophy and reduced chemoreceptor response.[3,17]

Respiratory patterns change at high altitudes due to the response of central and peripheral chemoreceptors to dynamic changes and patterns of oscillation of oxygen and carbon dioxide levels in the blood. Central sleep apnea is a feature that causes a sharp decrease in oxygen saturation during apnea and arousal (awakening phase of sleep) during hyperpnea in both highlanders and temporary immigrants. These are factors that contribute to severe hypoxemia leading to altitude-related illness (Figure 5).[5]

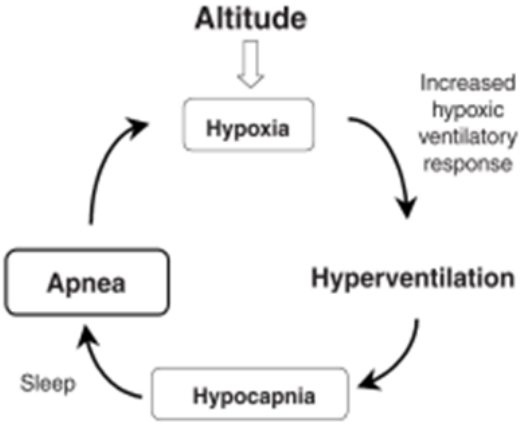

Figure 5. Mechanism of periodic breathing at altitude (High Alt Med Biol)

Diffusion

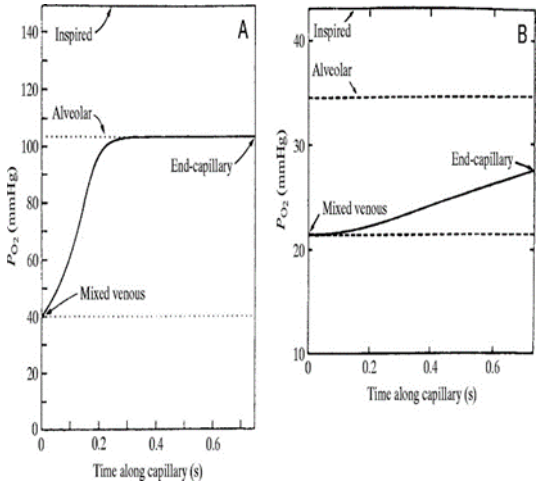

Figure 5. Mechanisms of diffusion at altitude and diffusion at sea level

Diffusion is decreased at high altitudes due to a decrease in the pressure gradient across the capillary-alveolar membrane, which cannot be compensated for even with an equilibrium time of 0.75 seconds. Further diffusion continues to decrease as the equilibrium time shortens (Figure 5). As a result, PaO_2 decreases and falls within the range that belongs to the steepest part of the oxygen dissociation curve. This results in a considerable decrease in the oxygen content of pulmonary capillary blood, even with a slight decrease in PaO_2. Highlanders who have been there for long periods of time have less differential arterial alveolar oxygen, better diffusion capacity, and higher PaO_2 averages than lowlands populations exposed to the highlands.[18]

Perfusion

Pulmonary circulation is a high-flow, low-pressure system. At altitude, the entire lung is hypoxic and hypocapnic. The vasomotor tone of the pulmonary vascular structure is mainly affected by the local effects of oxygen and carbon dioxide. When the oxygen concentration in the alveoli falls below normal, especially when it falls below 70% of normal (<73 mmHg PO2), adjacent blood vessels constrict, increasing vascular resistance more than fivefold. This contrasts with the effect on systemic blood vessels, which enlarge in response to low oxygen. This situation occurs because it is believed that low oxygen concentrations cause some unknown vasoconstrictor substances to be released from the lung tissue. These substances constrict the small arteries and arterioles. It has been suggested that this vasoconstrictor substance may be secreted by the alveolar epithelial cells during hypoxia. It has an important function which is to distribute the blood flow where it is most effective. Therefore if some of the alveoli are poorly ventilated so that the oxygen concentration becomes low, the local vessels will constrict and cause blood to flow through other areas of the alveoli, which are better, thereby providing an automatic control system to distribute blood flow to the lung areas in proportion to the alveolar oxygen pressure.[19,20]

Chronic hypoxia in highlanders causes structural changes (this has been studied in various species, including rats, goats, and humans, although resistance appears in some species) in the form of intimal fibrosis, smooth muscle hypertrophy, and collagen proliferation with *the remodeling* of vascular structures. A lung that cannot be reversed by correcting hypoxia. As a result, there is a sustained increase in resting pulmonary arterial pressure and pulmonary vascular resistance. The hallmark of this response to chronic hypoxia is the increased muscularization of the distal vessels with the addition of muscle to previously muscles arterioles.[20]

It may take weeks to months after return to sea level for right ventricular hypertrophy and pulmonary vascular pressure to normalize in such cases. Inhabitants of the Andean highlands have high pulmonary artery pressures, and descent to sea level or normal oxygen tensions does not return pulmonary artery pressures or right ventricular hypertrophy to normal levels. In contrast, the Tibet highlanders had minimal increases in pulmonary arterial pressure and did not exhibit the vascular changes exhibited by the Andes highlanders.[21]

Cardiac response

Studies in healthy people exposed to hypoxia have found resting heart rates and increased cardiac output in an attempt to maintain transport oxygen after 2 to 3 days of exposure to hypoxia, and stroke volume will decrease. Heart rate will remain high, so the cardiac output is maintained below sea level.[20]

Ascent to high altitude increases cardiac output by increasing heart rate without a concomitant increase in stroke volume. In fact, there is decreased stroke volume due to decreased plasma volume as a result of alkaline diuresis, natriuresis, and respiratory fluid loss due to hyperventilation. Myocardial depression, which can occur in severe hypoxia, is not a common cause of low stroke volume. In acute exposure to increased altitude, there is an increase in systemic blood pressure and an increase in vascular resistance due to increased sympathetic activity. Staying at high altitudes for long periods of time is likely to reduce peripheral vascular resistance due to the vasodilatory effect of hypoxia on peripheral circulation.[22]

Oxygen transport upon exposure to high altitude PaO2 is seen in the steep section of the oxygen dissociation curve showing a significant decrease in hemoglobin oxygen content (Hb) even with a slight decrease in PaO_2. To increase oxygen uptake in the lungs, the oxygen dissociation curve that determines blood oxygen content shifts to the left due to respiratory alkalosis caused by hypoxic hyperventilation. At the tissue level, the oxygen dissociation curve shifts to the right to facilitate the release of oxygen from Hb. This rightward shift is due to renal compensation for respiratory alkalosis and an increase in the concentration of 2,3-

diphosphoglycerate (2,3-DPG), shown in Figure 6.[3]

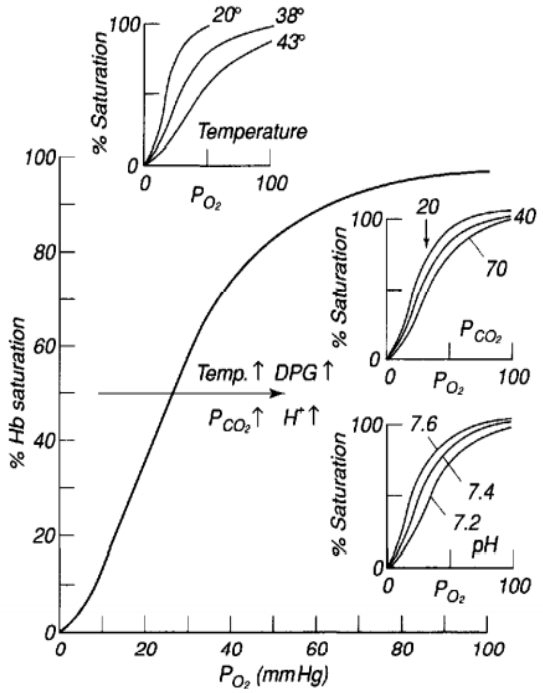

Figure 6. The oxygen dissociation curve is normal, and the oxygen dissociation curve shifts with increasing H+, PC02, temperature, and 2,3-diphosphoglycerate (DPG).

Acid-base response

Acid-base responses have been observed in highland climbers. The respiratory alkalosis produced by hypoxia at altitude increases the compensatory renal excretion of bicarbonate. This renal adaptation is completed within 24 hours at low to moderate altitudes. The time to reach a steady state for bicarbonate excretion is longer at higher altitudes and inhibits H^+ Blood gas analysis of 1865 residents living at 3510 meters found a normal PH.

Table 2. Normal values of blood gases of varying degrees of altitude

Altitude (m)	Barometric pressure	$PaCO_2$	PaO_2
Sea level	760	40	100
3510	495	30	60
6400	344	20.7	38.1
7440	300	15.8	33.7
7830	288	14.3	32.8
8848	253	7.5	29.5

Erythropoiesis

Exposure to hypoxia causes changes in oxygen affinity in the blood and stimulates red blood cell production in an effort to increase tissue oxygenation. Elevated levels of red blood cell 2,3-diphosphoglycerate have an allosteric effect on hemoglobin, reducing its affinity for oxygen and facilitating its release to tissues, despite impaired oxygen uptake when blood flows to the lungs. Increasing the size of red blood cells also has a negative impact because it will increase blood viscosity. Very little is known that an increase in blood

viscosity contributes to pulmonary arterial pressure, suggesting that an increase in pulmonary arterial pressure precedes an increase in hemoglobin.[20]

Hemoconcentration occurs on exposure to high altitudes. Within a few days after staying in the highlands, Hb levels increase due to increased erythropoiesis due to hypoxia-mediated release of erythropoietin from the kidneys. An increase in the oxygen content of the blood increases oxygen delivery.[23]

Highland-induced variability of erythropoiesis is observed in upland populations differently. Environmental and genetic factors have been linked to the same. Residents of Colorado and the Andean highlands showed significant erythrocytosis, while residents of the Tibetan highlands showed minimal or no erythrocytosis. The presence of excessive cobalt, as well as genetic factors, have been linked to these differences among the Andean highlanders. Polycythemia with a hematocrit above 60% has a deleterious effect on cardiac output and microcirculation due to an increase in blood viscosity.[7]

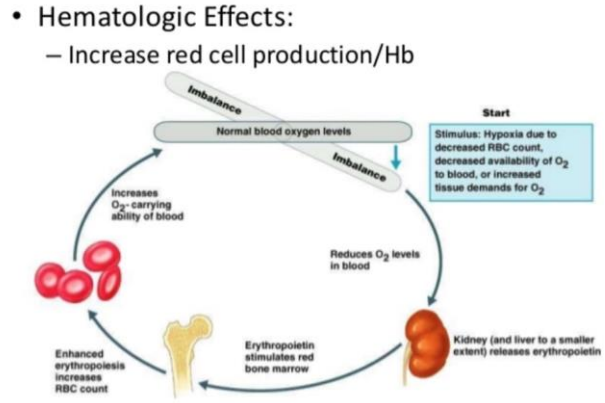

Figure 7. Hematological adaptation to hypoxia at altitude, the kidneys produce and secrete erythropoietin which stimulates the spinal cord to produce erythrocytes.

Highland adverse effects

Being at a sudden height and living there without adaptation is a risky thing with high susceptibility to High diseases and altitude-related diseases such as Acute Mountain Sickness (AMS), Cerebral Edema (HACE), and High-Altitude Pulmonary Edema (HAPE).[4]

The frequency increases with increasing altitude. Therefore the altitude we are at and also the speed of ascent, the physical conditioning, and associated morbidity, as well as individual vulnerability, are questionable. Young people, obese, and the elderly are easier to experience the disorders mentioned above. There are no specific markers to predict susceptibility, but individuals who exhibit a poor hypoxic ventilation response (HVR) are at higher risk.[24]

High altitude illness indicates a response to oxygen and descent to lowlands. These conditions have several overlapping features. This disorder can be prevented by avoiding undue physical exertion, gradual ascent, acclimatization, and drug prophylaxis. The incidence varies from 9% to 70% in different populations, such as trekkers, skiers, and armed forces personnel. High Altitude illness often poses a serious challenge to the health care system because immediate therapy is difficult to provide due to the lack of adequate medical facilities at the scene and obstacles in evacuating these cases to lower ground where treatment facilities are available. At high altitudes, HAPE and HACE are serious and can be fatal, with a mortality of up to 30%.[25,26]

2. Conclusion

Medical problems will arise when you are at a height due to a decrease in PaO_2 by a decrease in barometric pressure. The respiratory system plays an important role in adaptive and maladaptive responses to altitude. If there is a failure of adaptation, there is a risk of developing altitude sickness that can affect a person as a whole, including hematology, acid-base, kidney, and heart.

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