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Review Article

Identification Of the Effect Of Hyperbaric Oxygen Therapy (Hbot) On Blood Pressure Lowering Effects In Hypertension Patient

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ABSTRACT

Hypertension is a leading cause of death worldwide including in Indonesia. The World Health Organization (WHO) estimates that currently the global prevalence of hypertension is 22% (WHO, 2019). In 2018 the prevalence of hypertension in Indonesia reached 34,11% (Riskesdas, 2018). Every year, it is estimated that 10.4 million deaths are caused by hypertension (Unger et al., 2020). Hyperbaric Oxygen Therapy (HBOT) is a therapy with pure oxygen concentration (100%) in a high pressure room (Ortega et al., 2021). In previous studies it was found that HBOT improves the effects of vasodilation (Mihaljevic et al., 2018). However, other studies mention different results. It was found that HBOT initiates vasoconstriction and increases systemic vascular resistance. This causes a decrease in nitrite oxide (NO) production and increase NO oxidation (Goyal et al., 2021). Apart from a variety of different study results, the use of HBOT has indeed been widely studied even though it has not found a clear meeting point on the effects of blood pressure reduction on hypertension patients. Therefore, the author aims to find out more clearly the mechanism and benefits of hyperbaric oxygen therapy against decreased blood pressure in hypertension patients.

Introduction

Hypertension is one type of non-infectious disease which is one of the most causes of premature death in the world including in Indonesia. The World Health Organization (WHO) estimates that currently the global prevalence of hypertension is 22% of the world's total population (WHO, 2019). Every year, it is estimated that 10.4 million deaths are caused by hypertension. In developed countries the hypertension is estimated to be experienced by 349 million people, while in developing country groups the amount tends to be higher, which is 1.04 billion people (Unger et al., 2020). The results of Riskesdas 2018 showed the prevalence of hypertension in the population of >18 years in Indonesia reached 34.11%, this amount increased compared to 2013 by 25.8% (Riskesdas, 2018).

Hypertension is a condition where a person's blood pressure is higher than normal blood pressure, that is, if systolic blood pressure is ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg at periodic checks (Unger et al., 2020). Hypertension is a disease that can cause various complications, as well as being the disease that causes the most death and disability worldwide (Whelton et al., 2017).

Hyperbaric Oxygen Therapy (TOHB/HBOT) is a therapy with pure oxygen concentration (100%) in a high pressure room with a minimum size of 2 ATA (Ortega et al., 2021). In previous studies conducted by Martinelli et al., (2019) found that hyperbaric oxygen therapy increased changes in the cardiorespiratory system. In similar studies, it was found that hyperbaric oxygen therapy improves the effects of vasodilation through changes in ROS, increased antioxidant genes, and antioxidative enzymes (Mihaljevic et al., 2018). In addition, increased relaxation is most likely due to hyperbaric oxygen therapy modulating the activation of the CYP450 epoxygenase pathway from arachidonic acid metabolism and increasing the formation and sensitivity to epoxyeicosatrienoic acid (EET). In addition, HBOT enhances the expression of Hypoxia-inducible factor 1-alpha (HIF-1α), which stimulates COX expression and prostacyclin formation (Mihaljevic et al., 2020).

However, other studies mention different results. Research conducted by Goyal et al., (2021) mentions that HBOT initiates vasoconstriction and increases systemic vascular resistance. This causes a decrease in nitrite oxide (NO) production in the endothelium to increase NO oxidation. In addition, HBOT causes changes in vasodilator compounds (prostaglandins) and contributes to central vasoregulation which causes stimulation to sympathetic nerves to increase vasoconstriction (Goyal et al., 2021).

Apart from a variety of different study results, the use of HBOT has indeed been widely studied even though it has not found a clear meeting point on the effects of blood pressure reduction on hypertension patients. Therefore, the author aims to find out more clearly the mechanism and benefits of hyperbaric oxygen therapy against decreased blood pressure in hypertension patients.

Discussion

Hypertension is defined as an increase in blood pressure, if systolic blood pressure is valued at ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg at periodic examinations (Unger et al., 2020). The mechanism of occurrence of hypertension can be affected by disorders of cardiac output, peripheral resistance, Renin-Angiotensin-Aldosterone System (RAAS), microvascular changes, inflammation, and insulin sensitivity (Saxena et al, 2018). Disorders of vascular function in hypertension are characterized by arterial remodeling, cell dysfunction, increased vascular contraction, and fibrosis (Jia et al, 2018). Arterial constriction due to cardiac dysfunction will be effective against increased peripheral resistance, whereas both peripheral blood vessels and cerebral circulation are affected by increased cardiac output; both play an important role in regulating blood pressure (Batool et al, 2018).

Microvascular changes cause perfusion disorders that can cause ischemia or rupture of blood vessels and have a long-term effect on organs (Batool et al, 2018). Endothelial cell disorders due to impaired release of relaxation factors (NO) and contractions (endothelin) which are followed by increased proinflammatory, prothrombotic factors, as well as growth factors and decreased levels of NO by superoxide and ROS causes are thought to play a large role in the occurrence of hypertension (Saxena et al, 2018). The presence of ROS also

causes vascular modification due to cell lysis. In addition, the presence of inflammation will bring in cytokine, chemokine, and prostaglandin E (PGE) mediators which can stimulate thickening of the walls of blood vessels causing hypertension. In diabetics, insulin disorders can cause a decrease in glucose levels to the tissue which causes a decrease in NO and an increase in inflammation to oxidative stress (Batool et al, 2018).

High levels of the renin enzyme as an extra cell volume regulator and arterial vasoconstriction will increase blood pressure. Renin converts angiotensinogen to angiotensin I then angiotensin-converting enzyme (ACE) will convert it to angiotensin II which also has an effect on the arteries, increased peripheral resistance, and blood pressure; angiotensin II can stimulate aldosterone to increase water and salt resorption so that blood volume and blood pressure increase through RAAS activation (Saxena et al, 2018). Cyclooxygenase 2 (COX-2) and p66Shc signaling are involved in the activation of NADPH oxidase-induced angiotensin II (NOX), one form of reactive oxygen species (ROS). Increased NOX decreases NO bioavailability which then interferes with endothelium-dependent relaxation including heart function which can trigger heart muscle stiffness and diastolic dysfunction (Jia et al, 2018). In addition, prostanoids are produced from the activation of COX-1 by ROS as another cause of endothelial dysfunction (Qoth'i et al, 2021).

Hyperbaric oxygen therapy (HBOT) is a therapy performed in hyperbaric chambers with pressures of more than 1 absolute absolute (ATA) while breathing 100% pure oxygen. Variation in the duration of therapy is around 1.5-2 hours and can be done up to 60 times the therapy depending on the indication (LAM et al, 2017). There are at least some HBOT indications for clinical recognition by the Undersea and Hyperbaric Medical Society USA, namely gas or air embolism, gangrene gas, problems with skin grafts and flaps, decompression sickness, wound, anemia, intracranial abscess, soft tissue necrotizing infection, radiation tissue damage, osteomyelitis refractory, sensorineural deafness, thermal burns, crush injury, compartment syndrome, acute ischemic by trauma, and intoxication (carbon monoxide, carbon dioxide, cyanide (Jain, 2016). Untreated tension pneumothorax is an absolute contraindication of HBOT, other contraindications are relative with regard to benefitting or harm to patients (Jain, 2016). HBOT has an effect on mild but not clinically significant blood pressure improvement except in patients with low ejection fraction or severe stenosis (Heyboer et al, 2017).

Hyperbaric oxygen therapy (HBOT) has three main principles, namely the occurrence of positive pressure due to inhalation of 100% O2 (occurring diffusion into hypoxic tissue); increased concentration of O2 in the blood; and reduction in blood gas bubble size. Based on these three principles, hyperbaric conditions with pure oxygen condition the body in a state of hyperoxemia and hyperoxia without involving hemoglobin (Ortega et al, 2021). Hyperoxic-hypoxic is an event due to intermittent exposure to hyperoxia that causes a cellular mechanism and mediator by hypoxic induction, but if hyperoxia is given short term it will benefit the cell (Ortega et al, 2021). In a state of tissue hypoxia, HBOT provides an oxygen supply that will increase ROS and RNS as signaling pathways to decreased inflammation, matrix formation, and neovascular formation (Lam et al, 2017). Together with extracellular regulated kinase (ERK1/ERK2) will improve the regulation of hypoxia-inducible factors (HIF) (Ortega et al, 2021). Increased ROS and RNS production also affect cytokine prostaglandins, and NO tissue. So that HBOT has a response to injury, surgery, and infection. The suppression of proinflammatory

cytokine production by HBOT will affect the production of necrosis factor-α (TNF-α) tumors, endothelin, increased vascular endothelial growth factor (VEGF), while PGE2 and COX-2 mRNA decrease (Rosyanti et al, 2019). The formation of extracellular matrices by HBOT supports migration and proliferation by fibroblast growth factors so as to stimulate collagen-crosslinking to improve bonds between tissues (Lam et al, 2017).

Increased NO production and endothelial progenitor cells accelerate wound healing by accelerating angiogenesis (neovascularization) and epithelialization. In animal models, this is supported by the findings of the regulation of tumour necrosis factor-α (TNF-α), matrix metallopeptidase 9 (MMP-9) and tissue inhibitors of metalloproteinase-1 (TIMP-1). Increased VEGF, interleukin-6 (IL-6), and decreased endothelin-1 also support wound healing and angiogenesis (Ortega et al, 2021). In addition, HBOT plays a role in suppressing proinflammatory mediators (TNF-α, IL-6 and IL-10); against immunity, HBOT alrerates CD4:CD8 T cell ratio, and triggers apoptosis of neutrophil cells as well as lymphocytes (Memar et al, 2019); and other proinflammatory mediators including IL-1β, IL-8, IFN., 2021). According to several studies, neovascularization by HBOT occurs because increased oxygen levels can increase NO including in the bone marrow which then increases the mobility of progenitor cells to stimulate more cell stems and form new blood vessels (LAM et al, 2017).

Hypertension can be caused by several pathophysiological mechanisms, one of which relates to RAAS, where one that plays a role is the hormone angiotensin I and II. In hypertension therapy, angiotensin-converting enzyme (ACE) inhibitor drugs inhibit changes in the formation of angiotensin II as a vasoconstrictor (Goyal, Cusick, and Thielemier, 2021). The same mechanism is also obtained in herbal medicine, where the flavonoid content of the God's Crown inhibits ACE (Abed, 2020). This shows the important role of the hormone angiotensin in hypertension therapy. In this case, HBOT therapy also utilizes the hormone angiotensin II to increase the expression of visfatin which plays a role in increasing angiogenesis (Chiu et al, 2020). Whereas, in hypertension, the angiogenesis process undergoes interference as the body's response to the isocapnic hypoxia state (Garcia et al, 2020). Thus, the production of visfatin stimulated by the hormone angiotensin II along with the JNK pathway can improve the process of disturbing angiogenesis as a result of hypertension (Chiu et al, 2020).

Under conditions of hypertension, the body will activate heme oxygenase-1 (HO-1) in response to inflammation and oxidative stress that occurs (Martínez-Casales, Hernanz and Alonso, 2021). Although it is not enough to repair the damage from the effects of hypertension, HO-1 plays an important role in the regulation of blood pressure and vascular homeostasis in hypertension conditions (Martínez-Casales, Hernanz and Alonso, 2021). In the study of rats with post-ischemic acute kidney injury (MMR) conditions, HBOT therapy acts as a stronger stimulator that can increase HO-1 activity and cytoprotective effects, even in hypertension conditions (Nesovic Ostojic et al, 2021).

Damage to blood vessel resistance can be stimulated by oxidative stress stimulation which causes endothelial dysfunction and directs to hypertension conditions. The dysfunction endothelium then activates inflammatory cells (Masi, 2020). The inflammatory process will stimulate thickening or change of blood vessels (Batool et al, 2018; Jia et al, 2018). Expression of pro-inflammatory factors is also supported by the hormone angiotensin II and aldosterone through

RAAS (Jia et al, 2018). Proinflammatory cells in hypertension are intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), interferon-γ (IFN-γ), TNF-α, interleukin (including IL-1, IL-6, IL-8, IL-17, IL-23). The production of IL-6's specific interleukin changes vascular permeability and contraction (Tanase et al, 2019) TNF-α is prohypertension (Guzik and Touyz, 2017). NF-κB mediates the stiffness of arterial blood vessels as well as the heart (Jia et al, 2018).

Against inflammation, HBOT inhibits proinflammatory mediators, namely IL-1β, IL-6, IL-8, IFN-γ, NF-κB and TNF-α (De wolde et al, 2021). Obstacles to IL-1 and TNF-α will also reduce the effect of endothelin as a vasoconstrictor (Tanase et al, 2019). Based on this mechanism, HBOT might work well in overcoming inflammation as a cause of pathophysiology and preventing its continued effect on blood vessels in hypertension. Another mechanism is in the form of excess ROS production which can cause oxidative stress and have an impact on endothelial dysfunction, through increased peripheral resistance, vasoconstriction, and vascular remodeling (Konokoglu and Uzun, 2016). This is because oxidative stress can reduce the amount of NO which is a factor affecting the vasodilation of blood vessels (Prado et al, 2021). In addition, increased ROS can increase matrix metalloproteinase (MMP) which increases vasoconstriction (Prado et al, 2021). HO-1 activity can reduce the amount of ROS in the body. With HBOT, HO-1 activity will increase and the body can be protected from the effects of damage due to hypertension (Nesovic Ostojic et al, 2021). In addition, through the mechanism of angiogenesis enhancement, HBOT has a positive impact on hypertension by increasing NO production and other angiogenic factors, such as epidermal growth factor (EGF), VEGF, and endothelin-1 (Ortega et al, 2021).

Thus, through various mechanisms that have been described, HBOT has a positive impact on hypertension. However, HBOT therapy has effects that lead to an increase in blood pressure. In studies related to the effect of HBOT therapy on blood pressure, an increase in arterial blood pressure, especially systole (SAP), was up to 9.8% (Schiavo et al, 2020). This phenomenon is clinically significant in people who have a history of hypertension, but it is also obtained in people with normotensive. One of the alleged causes of increased post HBOT blood pressure is the vasoconstriction response (Schiavo et al, 2020). In other studies, HBOT therapy caused an increase in vascular oxidative stress in the form of superoxide compounds which had an impact on vasorelaxation disorders (Mihaljević et al., 2018). When comparing the effects of acute and gradual HBOT therapy, the effects of vasoconstriction and vasorelaxation disorders are only obtained on acute therapy. Similar to its effects which run very fast and are temporary. Whereas in gradual therapy, HBOT can more effectively reduce ROS, increase the expression of antioxidant genes, and increase the activity of antioxidative enzymes (Mihaljević et al., 2018). Although vasoconstriction effects are not obtained on gradual therapy, blood pressure checks before HBOT must still be carried out to avoid harmful effects (Schiavo et al, 2020). Research related to the effects of HBOT therapy on hypertension in humans has not been widely found. However, more animal studies can provide a new scientific view of the opportunities for HBOT therapy in more practical hypertension, so further studies are needed regarding the effect of HBOT on blood pressure in humans.

Conclusion

Hyperbaric oxygen therapy has an effect on reducing blood pressure in hypertension patients through improved angiogenesis processes, increased HO-1 activity, and the inhibition of pro-inflammatory mediators. However, this can happen through a series of therapy sessions and there is not much evidence to suggest that it will have a significant impact if only one therapy is done. As for, patients who take hyperbaric therapy require further follow-up by a doctor to analyze changes in symptoms in the cardiovascular system. In addition, prevention related to hypertension risk factors is also very important in addition to patients being required to continue to undergo a healthy diet and life. Therefore, further research is needed regarding the effect of HBOT therapy on reducing blood pressure on hypertension, which is clearly known for its effectiveness.

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