Macrophage polarization is related to the pathogenesis of decompression induced lung injury

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Abstract

Studies have shown that blood bubbles may be detectable and there is ultrasonic evidence of acute interstitial lung edema even after diving without protocol violation. Macrophages play a central role in the inflammation, and macrophage polarization is closely related to the pathogenesis some lung diseases. Available findings indicate that decompression may induce the production of pro-inflammatory cytokines, chemokines, and adhesion molecules in the blood and tissues, which are associated with the macrophage polarization, and hyperbaric treatment may exert therapeutic effects on decompression related diseases via regulating these factors. Thus, we hypothesize that the polarization of circulating and/or resident macrophages is involved in the pathogenesis of decompression induced lung injury.

Key words: decompression; lung injury; macrophage; polarization; bubble

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INTRODUCTION

The exposure to hyperbaric conditions may incur an inert gas load, and a state of inert gas supersaturation will be achieved in the blood and tissues when the inert gas tension (concentration/solubility) exceeds ambient pressure during the subsequent decompression. Thus, inert gas bubbles may form under this condition. The presence of bubbles in the blood vessels and tissues is a major cause of decompression sickness (DCS), though it does not correlate directly with clinical manifestations.¹,²

Of all the sites where bubbles form from supersaturated dissolved gas, most is known about bubbles in the veins. It is widely accepted that: (1) Generally, the amount of bubbles in tissues and circulation is related to the severity of DCS though there is individual difference; (2) The low amount bubbles might also cause severe DCS if they embolize important vessels. Bubbles forming in the veins may exert mechanical and biochemical effects in the blood, directly or indirectly activating leukocytes in the blood and subsequently resulting in inflammation.³,⁴ It is well known that lung is directly affected by the high oxygen partial pressure during diving. Moreover, the lung as a filter for microbubbles is also a target organ of bubbles secondary to decompression.⁵,⁶ With the development of ultrasound technique, increasing studies reveal that not only rapid decompression may cause the production of bubbles in the blood and tissues, but there are a small amount of bubbles in the blood vessels of divers after diving without protocol violation.⁷,⁸ Although clinical symptoms are not present in these divers, ultrasound examination shows the evidence of acute interstitial lung edema.⁹,¹⁰

Macrophages derived from mononuclear phagocytes (MP) are an important participant in the inflammatory reaction. Under the influence of the different microenvironments, the migrated monocytes give rise to a variety of MP subtypes, including mucosal macrophages, dendritic cells, and tissue-associated Langherans cells of skin, perivascular
macrophages, Kupffer cells of liver, and brain microglial cells.11 Macrophages may be activated along two main functional pathways. Pro-inflammatory stimuli result in classically activated macrophages or M1-cells, which participate in the clearance of either infected or transformed cells, but simultaneously contributing to tissue destruction. Conversely, anti-inflammatory signals induce alternatively activated or M2-macrophages that will activate cellular programs, promoting tissue regeneration and wound healing. This is also known as the macrophage polarization.12 Interferon-γ (IFN-γ)/lipopolysaccharide (LPS), tumor necrosis factor-α (TNF-α) and other factors may induced the M1 phenotype of macrophages which then produce reactive oxygen species (ROS), reactive nitrogen species (RNS), TNF-α, interleukin (IL)-1, IL-12, IL-23 and other chemokines. However, IL-4/IL-13, IL-10 and transforming growth factor-β (TGF-β) may induced the M2 phenotype of macrophages which then secrete TGF-β, vascular endothelial growth factor (VEGF), epithelial growth factor (EGF) and other growth factors.

**ROLE OF MACROPHAGES IN LUNG DISEASES**

Studies have confirmed that macrophages play important roles in the pathogenesis of some lung diseases.13 Macrophages account for about 3% of cells in the lung. There are a variety of receptors on the lung macrophages which can sensor and promptly respond to the damage. The activation of lung macrophages may secrete some pro-inflammatory cytokines (such as IL-1β and TNF-α) and induce the production of chemokines and adhesion molecules by other cells, involving the early lung injury.14 In addition, the phenotype of lung macrophages will change after phagocytosis of apoptotic cells, leading to the reduced production of pro-inflammatory cytokines and elevated production of anti-inflammatory cytokines, which is involved in the protective effects of macrophages in late stage of lung injury. In the process of lung injury, not only resident macrophages are involved in the pathogenesis of lung injury, but circulating macrophages will also be activated and then migrate into the lung due to chemotaxis, involving in the lung injury and repair. In lung injury, on one hand, some cytokines produced in the blood may activate circulating monocytes-macrohages and induce the expression of chemokine receptors on these cells; in the presence of a large amount of chemokines produced in the lung, these activated circulating monocytes-macrophages may migrate into the lung, involving the early inflammation of lung injury. On the other hand, a large amount of cytokines produced in the lung after injury may also induce the change in phenotype of resident macrophages, involving the lung injury and repair.15

**EVIDENCE ON THE ROLE OF MACROPHAGES IN DCS INDUCED LUNG INJURY**

Decompression may induce the switch of macrophage phenotype

Clinical trials have revealed that diving activities with routine decompression may still induce the activation of neutrophils and platelets in the blood.3,16 In rats with acute DCS, pro-inflammatory cytokines (such as TNF-α, IL-6 and IL-1β) increased significantly in the lung, accompanied by the elevation of circulating pro-inflammatory cytokines (TNF-α, IL-6 and IFN-γ).17,18 As above mentioned, TNF-α and IFN-γ are two major cytokines inducing the M1 phenotype of macrophages. Thus, we assume that decompression may induce the switch of macrophage phenotype in the blood and lung. However, whether bubbles produced in the veins directly induce the switch of macrophage phenotype and/or bubbles induce the production of relevant cytokines by other cells to indirectly activate macrophages is still unclear. During the decompression, vascular endothelial cells and resident cells of the blood are first group of cells encountering bubbles in blood vessels and affected directly by the decompression induced bubbles. In recent years, increasing studies focus on the influence of decompression-induced bubbles on vascular function and confirm that bubbles may cause damage to vascular endothelial cells, inducing vascular dysfunction.19-21 This has been validated in our studies.22,23 In addition, the improvement of vascular function was also found to be protective on DCS.24 Our study revealed that bubbles secondary to decompression could induce the production of microparticles22 which also induced the polarization of macrophages.25 In addition, microbubbles in the blood vessels may cause ischemia and subsequent alteration of vascular permeability, leading to the leakage of plasma.6 Under this condition, circulating pro-inflammatory cytokines may migrate into the lung and secret a large amount of pro-inflammatory cytokines, inducing the switch of macrophage phenotype. The platelets activated by bubbles16 may also produce a great deal of pro-inflammatory cytokines and chemokines to induce the activation, adhesion and chemotaxis of circulating monocytes-macrohages. Thus, it is possible that bubbles may act on vascular endothelial cells and/or platelets to indirectly induce the switch of macrophage phenotype.

Decompression induce adhesion and migration of macrophages

Studies have also revealed that the expression of intra-cellular adhesion molecule-1 (ICAM-1), E-selectin, L-selectin and MHC-II increased significantly in rats with DCS,16,17 which was confirmed by our study and found to be positively related to the decompression rate.22,23 More-
over, thromboxane and leukotriene B4 produced in blood also markedly increase following decompression, and leukotriene B4 has been confirmed as a potent chemokine of monocytes and may induce the invasion of monocytes into the lung.\textsuperscript{6,28} Furthermore, bubbles may also directly or indirectly increase the microvascular permeability, facilitating the chemotaxis of circulating monocytes-macrophages into the lung.\textsuperscript{6,28}

**Hyperbaric treatment affects the switch of macrophage phenotype**

A recent study indicates that hyperbaric oxygen may induce the shift of macrophage phenotype from M1 to M2.\textsuperscript{29} The spinal cord is relatively rich in lipid and thus susceptible to form bubbles after decompression. Generally, the spinal cord is also regarded as one of organs affected by DCS. Hyperbaric oxygen is one of treatments for DCS and has been widely used in the treatment of type I DCS or as an adjunctive therapy following hyperbaric treatment. Other studies also reveal that hyperbaric air treatment also increases the number of M2 macrophages in the muscle\textsuperscript{30}; hyperbaric oxygen may reduce the IL-6, matrix metalloproteinase-9 (factors produced by M1 macrophages) and macrophage inflammatory protein (an important chemokine), and increase the IL-10 (a factor inducing M2 phenotype)\textsuperscript{31,32} and IL-4.\textsuperscript{32} These findings indicate that hyperbaric treatment is able to regulate the macrophage polarization, which might be related to the therapeutic effects of hyperbaric treatment on DCS.

**Conclusion**

On the basis of available findings, we speculate that macrophage polarization is involved in the pathogenesis of decompression induced lung injury. Thus, treatments with the capability to regulate the phenotype of macrophages may exert protective effects on DCS and improve the outcome of DCS.

**Author contributions**

WWL designed this study and drafted the paper; CHH and PXZ searched and reviewed the literatures.

**Conflicts of interest**

The authors state that no conflicts of interest exist with this paper.

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