高原低氧环境下牙周炎的发病机制*

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摘要:牙周炎的病理过程受全身和局部因素的综合调控,一些调查研究显示高原牙周炎患病率高于平原地区,显然高原特殊环境在牙周炎的发生和发展过程中起到一定的作用,因此本文就高原低氧环境下牙周病变组织的变化、可能的发病机制作一综述。

关键词:高原;缺氧;牙周炎;病理

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Pathogenesis of Periodontitis in Anoxia and High Altitude Environment*

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ABSTRACT: The pathology of periodontitis is regulated synthetically by the whole and local elements of the body. Researches show that the prevalence of periodontitis in plateau is higher than in plain, obviously, the special environment in plateau is play some certain role during the genesis and progress of periodontitis. So this article is summarized on the changes of pathological periodontium, possible pathogenesis when exposed to anoxia at high altitude.

Key words: Plateau; Anoxia; Periodontitis; Pathology

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牙周病和龋病是口腔两大类首发疾病,在我国牙周病患病率更居龋病之上,约42.5%。我国高原人口众多,居世界首位,调查表明高原地区牙周炎患病率多达70.4%[1],显著高于其它地区。最新调查表明[2],随海拔高度和居住时间增加,牙周炎患病率呈上升趋势。

牙周炎是在病原体及其产物等作用下,刺激局部组织内免疫细胞大量浸润释放炎症介质,进一步激活宿主细胞释放炎症介质如细胞因子IL-1、TNF-α等,在大量炎性介质介导下造成牙周组织的降解和破坏[3-4]。高原的特殊环境变化主要是缺氧,使机体产生一系列调节性变化,这些变化影响着牙周组织的整个病理过程。

1 缺氧环境对牙周致病菌群的改变

牙菌斑是牙周病的始动因子,牙周常见致病菌伴放线放线杆菌参与启动牙菌斑的初期形成,牙龈卟啉单胞菌、中间普氏菌等可以在菌斑生物膜的基础上粘附定植,进而造成牙周组织破坏[5]。牙周炎的病理过程中,组织耗氧量增加,牙周袋底和组织氧含量降低。在高原环境下,机体各系统各器官都产生不同程度的缺氧,全身缺氧环境加重局部牙周组织缺氧,使厌氧菌生长繁殖加快,此外,缺氧使局部灌注不良加重组织水肿。低氧环境下,口腔内唾液分泌减少,口腔自洁功能减弱,加速了细菌的生长和菌斑的形成[6]。全身缺氧环境影响了病原体的生长和牙周组织的代谢,从而造成牙周组织的损伤。

有研究发现平原牙周炎的优势菌主要有福赛拟杆菌、牙龈卟啉单胞菌、脆弱拟杆菌、中间普氏菌,而高原低氧牙周炎的优势菌主要是牙龈卟啉单胞菌、中间普氏菌和伴放线放线杆菌,平原和高原的牙周致病菌的数量和不同种类的分布存在明显的差异,此外整个口腔微生态系也发生了改变,导致其他口腔疾病如口腔黏膜疾病等发生[7]。高压氧环境下,牙周袋的厌氧致病菌显著减少,病原体的种类明显改变,杆菌、梭状菌和螺旋体比率明显减少,牙周炎的严重程度也有所减轻[8-9]。组织的氧含量影响着微生物的增殖和分布,菌群数量和种类的改变在一定程度上加速了高原地区牙周炎的发生和发展。

2 缺氧环境对牙周组织的影响

2.1 缺氧对牙周组织的直接损伤作用

氧气是组织和细胞进行新陈代谢的关键物质,病理状态下,牙周组织和细胞因未得到充足氧发生代谢和功能障碍产生了损伤,全身缺氧加重了对牙周组织的直接损伤。

成纤维细胞是牙周膜中最常见的细胞,是牙周组织修复和改建的基础。有研究发现缺氧48小时,细胞功能活动的基础——线粒体和内质网等细胞器明显减少,成纤维细胞的代谢受到明显阻碍,相应地细胞发生了退行性变,溶酶体增多[10]。代谢的改变影响了细胞的裂解和凋亡,这种细胞毒作用直接破坏上皮组织的完整性。碱性磷酸酶(Alkaline phosphatase, ALP)是成纤维细胞分化成熟的标志。一些研究证实在缺氧状态下,成纤维细胞的ALP活性明显受到抑制,并且活性随缺氧时间而降低,缺氧抑制了细胞的生物学功能,成纤维细胞向成骨细胞和成牙骨质细胞分化的能力降低,不利于牙周组织的改建[11-12]。

有研究表明,在缺氧状态下,牙周膜成纤维细胞有较强的

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生长和增殖活性，且这种活性与缺氧程度加深呈依赖性增强，缺氧再复氧的细胞增殖活性高于常氧组，但较缺氧时降低[11]。但也有研究指出早期缺氧时，细胞的生长和增殖活性增强，在48-72 小时后，成纤维细胞的生长和增殖明显受到抑制[12]。另有研究发现缺氧可以抑制成骨细胞的增殖，同时促进成骨细胞的凋亡[13]。究其缺氧状态下，细胞的增殖活性如何变化，Piret 等[14]指出这与细胞的缺氧的严重程度呈明显依赖性，细胞在感受缺氧刺激时产生特异的转录因子——缺氧诱导因子 1α (Hypoxia inducing factor, HIF1α) 在轻度和重度缺氧时通过促进 mac-1、血管内皮生长因子(Vascular endothelial growth factor, VEGF)和 p53 等的表达，发挥抑制和促进细胞凋亡的双向作用。

总之，缺氧对牙周组织的直接损伤作用主要表现在对组织细胞的细胞毒作用，改变细胞的生长代谢和增殖分化，影响牙周组织的改建和修复，从而加速和加重高原牙周组织的病变。

2.2 缺氧环境下牙周组织中炎性因子的改变

有关牙周炎的病理机制目前形成的观点是 :微生物及其产物的侵袭和机体放大的炎症反应导致牙周组织的破坏和损伤[3, 15]。组织的炎症损伤主要由一些细胞因子[3-4]、粘附分子[16-17]和趋化因子[18-19]介导，主要通过 NF-κB 和 MAPK[20-23]信号通路调节机体的炎症应答。

研究发现在缺氧状态下，牙周组织炎症反应较常氧状态下更为严重，上皮糜烂变性，结合上皮向根方迁移和增殖，大量炎细胞浸润，牙周膜间隙增宽，牙周膜纤维排列紊乱，牙槽嵴吸收程度较严重，骨吸收陷窝处有较多的破骨细胞[6]，牙周组织以及龈沟液中一些炎症介质如 TNF-α 、PGE2 等表达增加[24]。金属基质蛋白酶(Matrix metalloproteinases, MMPs)是一类蛋白水解酶，是降解细胞外基质的主要酶类，在牙周病变过程中起着重要作用，一方面直接降解牙周炎症部位的细胞外基质，一方面可以增强其它酶类的表达和活性 [25]。在缺氧状态下， 机体 MMPs 的活性增高，增强牙周组织细胞外基质的降解，从而加重牙周炎症程度[26]。机体过度增强的免疫应答加速了牙周结缔组织附着丧失和牙槽骨的吸收，加重了低氧状态下牙周组织的炎症程度。

有人基于实验研究提出了高海拔低氧环境下肺组织炎症可能的作用机制，即缺氧使氧自由基(Reactive Oxygen Species, ROS)增加，氧化压力的增加上调了在炎症应答中起重要作用 NF-κ B 信号通路，从而使前炎症细胞因子 IL-1、IL-6、TNF-α 和细胞粘附分子 ICAM-1、VCAM-1、P- 选择素等在组织中的表达增加，这改变了细胞膜通透性，导致组织炎症和血管渗漏[27]。

活细胞新陈代谢过程中会产生 ROS，炎症反应通常伴随着 ROS 的增加，尤其在缺氧和微循环障碍的情况下，氧化压力的变化导致细胞功能紊乱和血管损伤，加剧牙周炎的进展[28]。在牙周病的病理过程中，局部组织缺氧，中性粒细胞产生大量的 ROS，加剧组织和细胞的破坏[29]。ROS 不仅可以使脂质、蛋白、核酸过氧化，直接破坏牙周组织的结构和代谢，此外，还能作为间接细胞信使，诱导细胞因子炎症介质的释放[30]。同时，炎症应答过程中，细胞因子、生长因子、血管活性物质可以诱导 ROS 产生，ROS 氧自由基调节 PI3K/Akt 和 MAPK 信号通路中一些激酶的活性产生级联放大反应激活 NF-κB 信号通路，使血管结构重塑和功能改变，导致血管疾病的发生和进展[31-33]。此外，缺氧、细胞因子、激素和 NO 等刺激都可以激活 HIF1α 过表达[14]，启动相关基因的表达介导细胞凋亡，影响牙周组织的修复。因此，在缺氧状态下，牙周组织破坏的可能机制即 :一是缺氧环境有利于牙周致病菌的生长繁殖和侵袭破坏；二是组织缺氧加重，ROS 和 HIF1α 的大量产生，一方面直接损伤牙周组织，影响牙周组织的代谢和修复， 一方面上调了炎症的 NF-κB 信号通路，炎症介质在牙周组织中过表达，介导组织的免疫损伤，产生级联放大效应，进一步加重了牙周组织破坏和微血管循环障碍，从而加速了牙周炎病变的进程。

3 牙周病变与全身的相互影响

实验研究表明牙周病变与全身疾病密切相关，牙周病致病菌及其代谢产物如内毒素通过血液循环侵袭血管内皮细胞[34]，牙周病变局部一些升高的炎症介质可以释放入龈沟液和血液循环，导致循环中相关因子水平随之升高，牙周基础治疗后血中炎症介质水平降低[35-37]，此外，氧自由基的产生使外周血中脂质水平也增高[38]，这些都可能是牙周病与心血管疾病相关的致病机制。体外实验发现，缺氧牙周炎动物牙周组织、龈沟液和血清中相关因子表达和活性显著增加[6, 16, 26, 39]。缺氧环境下，牙周组织产生大量的炎症介质进入血液循环，影响全身的免疫反应和机体的健康状态。

在缺氧状态下，机体血液黏滞度增高，微循环血流减慢，血栓形成和血管管腔狭窄[40]，导致牙周组织供氧不足，这不仅有利于牙周致病菌的生长， 也降低了牙周组织的防御和修复能力，而且牙周组织长期缺氧状态下，无氧代谢增强，有害物质也随之增加。此外，高原环境气候寒冷干燥，口腔内不能保持正常的温度和湿度，加上一些营养物质的缺乏，削弱牙周组织的修复的能力。可见，高原地区缺氧环境下，全身变化与牙周病变相互作用，从而诱发或加重牙周病以及一些全身疾病。

综上所述，高原特殊环境主要是缺氧对牙周组织、全身代谢和免疫的影响，厌氧菌和牙周组织局部缺氧环境在牙周炎的形成和快速进展中起重要作用，有关缺氧对机体的分子调节机制以及机体的适应性应答和损伤还有待于深入研究。

参考文献(References)

[1] 张运华,曹桢吾. 4500 米高原 1000 名官兵牙周炎调查分析 [J]. 解放军预防医学杂志, 1995, 13(2): 150-151
Zhang Yun-hua,Cao Zhen-wu. The diagnosis of periodontitis among 1,000 officers and soilders at the height of 4,500 meters of plateau [J]. J Preventive Medicine of Chin PLA, 1995, 13(2): 150-151(In Chinese)

[2] 蒲东全,刘鲁川,宋远雄,等. 不同海拔高度部队驻军官兵牙周健康调查 [J]. 牙体牙髓牙周病学杂志, 2009, 1: 35
Pu Dong-quan, Liu Lu-chuan, Song Yuan-xiong, et al. An epidemiological study of periodontal diseases among the garrison troops at different altitudes [J]. Chin J Conserv Dent, 2009, 1: 35(In Chinese)

[3] Graves D. Cytokines that promote periodontal tissue destruction [J]. J Periodontol, 2008, 79(8 Suppl):1585-1591

[4] Stathopoulou PG, Benakanakere MR, Galicia JC, et al. The host cytokine response to Porphyromonas gingivalis is modified by gingipain [J]. Oral Microbiol Immunol, 2009, 24(1): 11-17

[5] Zijnge V, van Leeuwen MBM, Degener JE, et al. Oral biofilm architecture on natural teeth [J]. PLoS One, 2010, 5(2): e9321

[6] 孔燕,谭颖徽,张纲,等. 模拟高原条件下大鼠牙周炎模型牙周组织中 TNF-α , PGE2 的表达 [J]. 牙体牙髓牙周病学杂志, 2009, (5):

261-264
Kong Yan, Tan Ying-hui, Zhang Gang,et al. The expression of TNF-α and PGE2 in periodontal tissues of a rat model with periodontitis exposed to hypoxia at high altitude [J]. Chin J Conserv Dent, 2009, (5): 261-264(In Chinese)

[7] 肖娴,孔燕,张纲,等. 模拟高原低氧环境下大鼠牙周炎致病菌多样性的实验研究 [J]. 牙体牙髓牙周病学杂志, 2009, 19(9): 517-520
Xiao Xian, Kong Yan, Zhang Gang, et al. The pathogenic bacteria diversity of rat periodontitis in imitative plateau environment: an experimental study [J]. Chin J Conserv Dent, 2009, 19(9): 517-520(In Chinese)

[8] 陈铁楼,许兵,蔺世龙,等. 高压氧对人不同袋深牙周炎袋底菌斑的形态学影响 [J]. 口腔医学, 2000, 20(1): 24-25
Chen Tie-lou, Xu Bin, Lin Shi-long, et al. Morphology effects of HBO-on plaque in pocket botton of human periodontitis with different pocket deep [J]. Stomatology, 2000, 20(1): 24-25(In Chinese)

[9] 陈铁楼,刘景昌,蔺世龙,等. 高压氧对动物牙周袋底菌斑和厌氧菌的影响 [J]. 口腔医学, 2003, 23(5): 270-271
Chen Tie-lou, Liu Jing-chang, Lin Shi-long, et al. Effect of hyperbaric oxygen on subgingival plaque of experimental periodontitis in animals [J]. Stomatology, 2003, 23(5): 270-271(In Chinese)

[10] 张海元,刘鲁川,刘福玉,等. 缺氧对人牙周膜成纤维细胞增殖和超微结构影响的实验研究 [J]. 实用口腔医学杂志, 2009, 25(4): 509-512
Zhang Hai-yuan, Liu Lu-chuan, Liu Fu-yu, et al. Experimental studies of hypoxia on the proliferation ability and ulstrastructure of cultured human periodontal ligament fibroblasts [J]. J Practical Stomatology, 2009, 25(4): 509-512(In Chinese)

[11] 唐开亮,李纾,王建,等. 乏氧对人牙周膜细胞增殖和碱性磷酸酶活性表达的影响 [J]. 牙体牙髓牙周病学杂志, 2008, 18(8): 453-455
Tang Kai-liang, Li Shu, Wang Jian, et al. Effects of hypoxia on the proliferation and alkaline phosphatase expression of human periodontal ligament cells in vitro [J]. Chin J Conserv Dent, 2008, 18(8): 453-455(In Chinese)

[12] 张海元,刘鲁川,刘福玉,等. 缺氧对人牙周膜成纤维细胞增殖和碱性磷酸酶活性的影响 [J]. 牙体牙髓牙周病学杂志, 2009, 19(2): 81-83
Zhang Hai-yuan, Liu Lu-chuan, Liu Fu-yu, et al. Effect of hypoxia on the proliferation and alkaline phosphatase activity of cultured human periodontal ligament fibroblasts [J]. Chin J Conserv Dent, 2009, 19(2): 81-83(In Chinese)

[13] 姜华,王稚英,姚琦,等. 缺氧对成骨细胞增殖及凋亡的影响. [J]. 口腔颌面修复学杂志, 2005. 6(2): 81-83
Jiang Hua, Wang Zhi-ying, Yao Qi,et al. Hypoxia affects the osteoblasts proliferation and apotosis [J]. Chin J Prosthodontics, 2005, 6(2): 81-83(In Chinese)

[14] Piret JP, Mottet D, Raes M, et al. Is HIF-1alpha a pro- or an anti-apoptotic protein? [J]. Biochem Pharmacol, 2002, 64(5-6): 889-892

[15] Leone CW, Bokhadhoor H, Kuo D, et al. Immunization enhances inflammation and tissue destruction in response to Porphyromonas gingivalis [J]. Infect Immun, 2006, 74(4): 2286-2292

[16] Park HJ, Jeong SK, Kim SR, et al. Resveratrol inhibits Porphyromonas gingivalis lipopolysaccharide-induced endothelial adhesion molecule expression by suppressing NF-kappaB activation [J]. Arch Pharm Res, 2009, 32(4): 583-591

[17] Liu R, Desta T, Raptis M, et al. P. gingivalis and E. coli lipopolysaccharides exhibit different systemic but similar local induction of inflammatory markers [J]. J Periodontol, 2008, 79(7): 1241-1247

[18] Tanabe SI, Bodet C, Grenier D. Treponema denticola peptidoglycan induces the production of inflammatory mediators and matrix metalloproteinase 9 in macrophage-like cells [J]. J Periodontal Res, 2009, 44(4): 503-510

[19] Pradeep AR, Daisy H, Hadge P, et al. Correlation of gingival crevicular fluid interleukin-18 and monocyte chemoattractant protein-1 levels in periodontal health and disease [J]. J Periodontol, 2009, 80(9): 1454-1461

[20] Xu J, Wu HF, Estabelle SM, et al. NF-kappaB modulators in osteolytic bone diseases [J]. Cytokine Growth Factor Rev, 2009, 20(1): 7-17

[21] Vardar-Sengul S, Arora S, Baylas H, et al. Expression profile of human gingival fibroblasts induced by interleukin-1beta reveals central role of nuclear factor-kappa B in stabilizing human gingival fibroblasts during inflammation [J]. J Periodontol, 2009, 80(5): 833-849

[22] Garcia de Aquino S, Manzolli Leite FR, Stach-Machado DR, et al. Signaling pathways associated with the expression of inflammatory mediators activated during the course of two models of experimental periodontitis [J]. Life Sci, 2009, 84(21-22): 745-754

[23] Sun Y, Shu S, Zhang Ming-zhu, et al., Toll-like receptor 4 signaling plays a role in triggering periodontal infection [J]. FEMS Immunol Med Microbiol, 2008, 52(3): 362-369

[24] 孔燕,肖娴,张纲,等. 模拟高原条件下大鼠龈沟液中 TNF-α , PGE2, IL-8 与牙周炎的相关性研究 [J]. 实用口腔医学杂志, 2010, 26(5)
Kong Yan, Xiao Xian, Zhang Gang, et al. Relationship between inflammatory cytokines in gingival crevicular fluid and periodontal clinical status in periodontitis rat model when exposed to hypoxia at hiIgh altitude [J]. J Practical Stomatology, 2010, 26(5) (In Chinese)

[25] 赵筱芩,孟姝,吴亚菲,等. 基质金属蛋白酶 -2 和基质金属蛋白酶 -3 在大鼠牙周炎模型中的表达 [J]. 华西口腔医学杂志, 2006, 24(3): 202-205
Zhao Xiao-qin, Meng Shu, Wu Ya-fei, et al. Expression of MMP-2 and MMP-3 in periodontal tissues of rat periodontitis model [J]. West China J Stomatology, 2006, 24(3): 202-205(In Chinese)

[26] 孔耀,刘鲁川,周霞. 模拟高原缺氧对慢性牙周炎大鼠牙龈组织中基质金属蛋白酶 -2 活性的影响 [J]. 解放军医学杂志, 2010, (3): 330-332
Kong Yao, Liu Lu-chuan, Zhou Xia. Effect of simulated altitude hypoxia on the activity of matrix metalloproteinase-2 in gingival tissue of chronic periodontitis rat model [J]. Med J Chin PLA, 2010, (3): 330-332(In Chinese)

[27] Sarada S, Himadri P, Mishra C, et al. Role of oxidative stress and NF-kB in hypoxia-induced pulmonary edema [J]. Exp Biol Med (Maywood), 2008, 233(9): 1088-1098

[28] Lum H, Roebuck K. Oxidant stress and endothelial cell dysfunction [J]. American Journal of Physiology- Cell Physiology, 2001, 280(4): C719

[29] 曹采方. 牙周病学. [M]. 2 版, 北京:人民卫生出版社, 2003, 65-66.
Cao Cai-fang. Periodontology, [M]. the 2nd edition, Beijing, The People's Medical Publishing House, 2003, 65-66

(下转第 2593 页)

independent of Ras or the MST1/2 kinases [J]. Oncogene, 2004, 23 (19):3426-3433

[17] Li J, El-Naggar A, Mao L. Promoter methylation of p16INK4a, RASSF1A, and DAPK is frequent in salivary adenoid cystic carcinoma [J]. Cancer, 2005, 104(4):771-776

[18] Jones PA, Baylin SB. The epigenomics of cancer [J]. Cell, 2007, 128 (4):683-692

[19] Hesson LB, Cooper WN, Latif F. The role of RASSF1A methylation in cancer [J]. Dis Markers, 2007, 23(1-2):73-87

[20] Targosz HZ, Kunnev D, Hawthorn L, et al. Transformation of MCF-10A cells by random mutagenesis with frameshift mutagen ICR191: A model for identifying candidate breast-tumor suppressors [J]. Mol Cancer, 2008, 7:51

[21] Pijnenborg J, Dam-de Veen G, Kisters N, et al. RASSF1A methylation and K-ras and B-raf mutations and recurrent endometrial cancer [J]. Ann Oncol, 2007,18(3):491-497

[22] Kaira K, Sunaga N, Tomizawa Y, et al. Epigenetic inactivation of the RAS-effector gene RASSF2 in lung cancers [J]. Int J Oncol, 2007, 31 (1):169-173

[23] Endoh M, Tamura G, Honda T, et al. RASSF2, a potential tumour suppressor, is silenced by CpG island hypermethylation in gastric cancer [J]. Br J Cancer, 2005, 93(12):1395-1399

[24] Zhang Z, Sun D, Van do N, et al. Inactivation of RASSF2A by promoter methylation correlates with lymph node metastasis in nasopharyngeal carcinoma [J]. Int J Cancer, 2007, 120(1):32-38

[25] Calvisi DF, Ladu S, Gorden A, et al. Ubiquitous activation of Ras and Jak/Stat pathways in human HCC [J]. Gastroenterology, 2006, 130 (4):1117-1128

[26] Macheiner D, Heller G, Kappel S, et al. NORE1B, a candidate tumor suppressor, is epigenetically silenced in human hepatocellular carcinoma [J]. J Hepatol, 2006, 45(1):81-89

[27] Dreijerink K, Braga E, Kuzmin I, et al. The candidate tumor suppressor gene, RASSF1A, from human chromosome 3p21.3 is involved in kidney tumorigenesis [J]. Proc Natl Acad Sci USA, 2001,98 (13): 7504-7509

[28] Steiner G, Cairns P, Polascik TJ, et al. High-density mapping of chromosomal arm 1q in renal collecting duct carcinoma: region of minimal deletion at 1q32.1-32.2 [J]. Cancer Res, 1996, 56(21): 5044-5046

[29] Hesson LB, Dunwell TL, Cooper WN, et al. The novel RASSF6 and RASSF10 candidate tumor suppressor genes are frequently epigenetically inactivated in childhood leukaemias [J]. Mol Cancer, 2009,8:42

[30] Hubbard TJ, Aken BL, Beal K, et al. Ensembl 2007. Nucleic Acids Res, 2007, 35(Database issue): D610-D617

(上接第 2589 页)

[30] **张海元,刘鲁川. 氧自由基与牙周炎关系研究进展** [J]. **牙体牙髓牙周病学杂志**, 2009, 19(1): 46-49
Zhang Hai-yuan, Liu Lu-chuan. Progress on the relationship betwteen oxygen-derived free radical and periodontitis [J]. Chin J Conserv Dent, 2009, 19(1): 46-49(In Chinese)

[31] Ojaniemi M, Glumoff V, Harju K, et al. Phosphatidylinositol 3-kinase is involved in Toll-like receptor 4-mediated cytokine expression in mouse macrophages [J]. European journal of immunology, 2003, 33(3): 597-605

[32] Madrid LV, Wang CY, Guttridge DC, et al. Akt suppresses apoptosis by stimulating the transactivation potential of the RelA/p65 subunit of NF-kappaB [J]. Mol Cell Biol, 2000, 20(5): 1626-1638

[33] Fortuno A, San Jose G, Moreno M, et al. Oxidative stress and vascular remodelling [J]. Exp Physiol, 2005, 90(4): 457-462

[34] Ao L, Song Y, Fullerton D, et al. The interaction between myocardial depressant factors in endotoxemic cardiac dysfunction: role of TNF-alpha in TLR4-mediated ICAM-1 expression [J]. Cytokine, 2007, 38 (3): 124-129

[35] Teles RP, Sakellari D, Konstantinidis A, et al. Application of the checkerboard immunoblotting technique to the quantification of host biomarkers in gingival crevicular fluid [J]. J Periodontol, 2009, 80 (3): 447-456

[36] Vidal F, Figueredo CM, Cordovil I, et al. Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension [J]. J Periodontol, 2009, 80(5): 786-791

[37] **刘冰,李淑娟,黄香河,等. 牙周炎大鼠血清和牙龈组织中白细胞介素 -6 含量比较分析** [J]. **中国实用口腔科杂志**, 2010, 3(2): 100-102
Liu Bin, Li Shu-juan, Huang Xiang-he, et al. Comparative analysis of the levels of IL-6 in blood serum and gingival tissue of experimental periodontitis rats [J]. Chin J Practical Stomatology, 2010, 3 (2): 100-102(In Chinese)

[38] Tomofuji T, Sanbe T, Ekuni D, et al. Oxidative damage of rat liver induced by ligature-induced periodontitis and chronic ethanol consumption [J]. Arch Oral Biol, 2008, 53(12): 1113-1118

[39] **孔耀, 刘鲁川, 周霞, 等. 模拟高原缺氧对慢性牙周炎大鼠血清中 MMP-2 表达的影响** [J]. **第三军医大学学报**, 2010, (4): 324-326
Kong Yao, Liu Lu-chuan, Zhou Xia, et al. Effect of simulated high altitude hypoxia on matrix metalloproteinase- 2 expression in serum of rats with chronic periodontitis [J]. Academiae Medicinae Militaris Tertiae, 2010, (4): 324-326(In Chinese)

[40] **高钰琪.高原军事医学**. [M]. **重庆, 重庆出版社**,2005:6-8
Gao Yu-qi. Military Medicine at plateau, [M]. Chongqing, Chongqing Publishing Company, 2005:6-8