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单核细胞与高密度脂蛋白比值在心血管疾病中的研究进展

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[摘要] 心血管疾病的发生和发展与炎症反应和脂质沉积密切相关, 单核细胞的积累和高密度脂蛋白胆固醇的减低在其中发挥了重要作用。单核细胞与高密度脂蛋白胆固醇比值(monocyte to high density lipoprotein cholesterol ratio, MHR)是一种结合了炎症和抗炎的新型炎症反应标志物, 目前有研究报道其能够以实用、经济、快捷的方式评估心血管疾病(cardiovascular diseases, CVD)的发生、发展及预后。现就MHR与CVD的研究进展进行综述。

[关键词] 单核细胞; 高密度脂蛋白胆固醇; 单核细胞与高密度脂蛋白胆固醇比值; 心血管疾病

Advances in the study of monocytes to high density lipoprotein ratio in cardiovascular diseases

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Abstract The occurrence and development of cardiovascular disease is closely related to inflammation and lipid deposition, in which the accumulation of monocytes and the decrease of high-density lipoprotein play an important role. The ratio of monocyte to high density lipoprotein cholesterol (MHR) is a new inflammatory marker that combines inflammation and anti-inflammation. It has been reported that it can evaluate the occurrence, development, and prognosis of cardiovascular disease in a practical, economical, and rapid way. In this paper, the research progress of MHR and CVD is reviewed.

Keywords monocytes; high density lipoprotein cholesterol; monocytes to high density lipoprotein ratio cholesterol; cardiovascular disease

心血管疾病(cardiovascular diseases, CVD)是指由多种因素导致的一组疾病的合称, 主要包括冠状动脉粥样硬化性心脏病、高血压病、心律失常、瓣膜病、心肌病等。动脉粥样硬化(atherosclerosis, AS)是冠心病的病理基础, 主要包括内皮损伤、脂质沉积、氧化应激与血管慢性

低度炎症等, 单核细胞是动脉粥样硬化形成过程中促炎物质的主要来源, 高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)通过抑制巨噬细胞的迁移和LDL氧化以及胆固醇从这些细胞的流出, 通过中和单核细胞的促炎和促氧化剂作用, 从而表现出抗动脉粥样硬化作用。因

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此, 单核细胞的积累和HDL-C的降低可能参与了AS和CVD。Kanbay等^[1]首次报道了单核细胞与高密度脂蛋白胆固醇比值(monocyte to high density lipoprotein cholesterol ratio, MHR)增加与CVD有关。因此本文着重于综述单核细胞、MHR与CVD研究进展。

1 MHR与冠状动脉疾病

1.1 MHR与冠状动脉粥样硬化性心脏病

冠状动脉粥样硬化性心脏病(coronary artery disease, CAD)的基本病因是AS长期进展导致血管官腔狭窄或闭塞。CAD病死率极高, 其发生的基础与血管慢性炎症反应有关。Ganjali等^[2]在一项研究中发现: MHR水平升高与多种CVD不良预后相关, 并且预示着更严重的疾病和可能的进展。MHR是一种实用, 具有成本效益和高度预测性的CVD标记, 可以作为预测动脉粥样硬化发展和进展的便捷标志物, 而不是单个单核细胞计数或HDL-C水平。心肌桥(myocardial bridge, MB)是一种冠状动脉变体, 心外膜冠状动脉穿过心肌带。虽然MB通常被认为是良性的, 但一些患者仍会出现如心绞痛、急性心肌梗死、冠状动脉痉挛、心律失常、晕厥和心脏性猝死。在血管造影系列中, MB的发生率估计为0.5%~2.5%, 常累及左前降支。Enhos等^[3]对160例冠状动脉正常的MB患者按MHR值分为MHR分为低(8.25 ± 1.61)、中(13.11 ± 1.46)、高(21.21 ± 4.30)三分位数研究, 发现MB组的MHR明显高于冠状动脉正常的对照组。MB的频率随着MHR频率的增加而增加。以单核细胞/高密度脂蛋白比值为临界点, 准确预测MB的敏感性为59%, 特异性为65.0%, 提示MHR与MB显著相关。

1.2 MHR与冠状动脉支架后血流的关系

慢冠状动脉血流(slow coronary flow, SCF)是指冠状动脉造影未发现官腔有明显狭窄, 但出现了远端血管灌注延迟。以往的研究表明, 炎症、氧化应激和内皮功能受损在SCF的发生中都起着重要作用^[4]。Kalyoncuoglu等^[5]将426名急性非ST段抬高型心肌梗死(acute non-ST-segment elevation myocardial infarction, NSTEMI)患者按经皮冠状动脉介入术(percutaneous coronary intervention, PCI)后心肌梗死溶栓血流分级进行分组, 发现慢复流组MHR明显高于非慢复流组($P < 0.01$), MHR可作为NSTEMI患者PCI术后发生慢复流的有用炎症生物标志物。冠状动脉无血流(no coronary reflow phenomenon,

NR)指PCI或静脉溶栓后, 心外膜闭塞动脉开通后, 梗死动脉支配的区域心肌组织出现无灌注或灌注不良的情况。Kalyoncuoglu等^[5]对经PCI治疗的NSTEMI患者研究发现: 高MHR、高心率、可作为无复流现象的独立预测因素。MHR是简单、廉价的标志物, 可以帮助预测慢/无血流的发展。然而, 为了评估MHR预测慢/无复流现象发展的准确性, 还需要进一步的大规模和前瞻性研究。

1.3 术前MHR与急性STEMI PCI

急性ST段抬高型心肌梗死(ST-segment elevation myocardial infarction, STEMI)作为一种病死率极高的疾病, 严重威胁人们健康, 而PCI是治疗STEMI的首选措施之一。目前有研究^[6]报道了MHR对STEMI患者PCI后有重要预测作用。Sercelik等^[7]对接受PCI的111例STEMI患者多因素logistic回归分析发现: MHR是急性STEMI和高TIMI评分的唯一独立预测因子。MHR是一种新的基于炎症的标志物, 可能是STEMI患者未来心血管事件的独立预测因子。Çağdaş等^[8]研究发现: MHR是SYNTAX评分评估STEMI患者冠状动脉疾病严重程度方面的独立预测因子。Wu等^[9]研究显示: MHR是接受PCI的CAD患者全因病死率和主要不良心脏事件(major adverse cardiovascular events, MACE)的独立预测因子。Villanueva等^[10]的一项荟萃分析发现直接PCI的STEMI患者入院时的高MHR与较高的住院病死率和MACE相关。这种新的标志物可以作为一种廉价且容易获得的风险分层工具。然而, 尽管存在显著相关性, 但仍应进行更大样本的研究以评估其在接受原发性PCI的STEMI患者中的临床效用。造影剂肾病(contrast-induced nephropathy, CIN)是急性冠状动脉综合征(acute coronary syndrome, ACS)患者经PCI术治疗后常见的并发症。Sağ等^[11]对209例PCI治疗的STEMI患者行多因素logistic回归分析显示: MHR与CIN独立相关, 较高的MHR水平预示着PCI后AMI患者CIN的发生。Ulus等^[12]对647名PCI术后的ACS患者分析发现年龄、糖尿病、对比度、估计的肾小球滤过率和MHR是CIN的独立预测因子, 术前MHR可作为CIN的简单标志物, 这可能有助于早期识别接受PCI的ACS患者。

2 MHR与非勺型高血压病

高血压病是CVD的主要和常见危险因素之一, 高血压通常伴有内皮功能障碍, 增加氧化应

激和血管并发症。MHR与高血压患者的靶器官损害有关^[13]。Selcuk等^[14]对108名原发性高血压患者分为非勺型高血压(non-dipper hypertension, NDHT)组56例, 勺型高血压(dipper hypertension, DHT)组52例研究, 结果显示: NDHT组的平均心率明显高于对照组和DHT组。MHR, hs-CRP和红细胞分布宽度是非勺型高血压的独立预测因子。在ROC分析中, MHR曲线下面积为0.62, hs-CRP曲线下面积为0.61, 提示非勺型高血压患者MHR水平升高。MHR水平升高可评估为非勺型高血压患者发生心血管事件的风险增加。Kaplan等^[15]研究报道: NDHT组局部尿白蛋白、肌酐、蛋白值、蛋白/肌酐比值均显著高于DHT组。NDHT组左心室肥厚和视网膜病变的发生率也较高。左心室肥厚伴视网膜病变者的平均心率明显高于无并发症者。提示MHR简便、无创、计算简单, 可用于预测高血压患者的终末器官损害(左心室肥厚、视网膜病变和蛋白尿), 也可用于区分DHT和NDHT组。

3 MHR与代谢综合征

代谢综合征(metabolic syndrome, MetS)是多种代谢成分异常凝聚的病理状态, 是导致糖尿病和CVD的危险因素。多囊卵巢综合征(polycystic ovary syndrome, PCOS)不仅与月经不调、不孕不育等短期后果有关, 而且还与长期事件包括肥胖、高血压、血脂异常和胰岛素抵抗有关, 这些都被认为是MetS的标志性成分^[16]。多发性硬化症与CVD、脑卒中和2型糖尿病风险增加相关。此外, 患有多囊卵巢综合征的女性患多发性硬化症的风险很高。Dincgez等^[17]研究PCOS患者的血清MHR对MetS的预测作用, 发现MHR在MetS组中较高。在多变量回归分析中, MHR比率是研究组多发性硬化的独立预测因子。MHR可能有望在PCOS早期预测MetS, 通过改变生活方式或给予药物治疗来预防未来的CVD。

4 MHR与阻塞性睡眠呼吸暂停伴发CVD

阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)是一种常见的疾病, 其特征是反复出现上气道的部分或全部阻塞, 导致低通气或呼吸暂停。OSA是CVD的独立危险因素^[18]。慢性气道塌陷会导致反复缺氧, 进而增加交感神经激活、氧化应激、全身炎症和内皮功能障碍。系统性炎症和随

后的血管损伤被认为是导致阻塞性睡眠呼吸暂停低通气综合征心血管发病率的潜在机制。Li等^[19]研究发现: MHR水平与呼吸暂停低通气指数呈正相关, 与最低SpO₂呈负相关($P < 0.01$)。OSA伴心血管病患者的MHR值明显高于无心血管病患者($P < 0.001$)。MHR与OSA的严重程度及心血管病的发生密切相关。MHR作为一种简便有效的检测方法, 有望成为预测中国汉族OSA患者心血管病的一种有前途的生物标志物。

5 MHR与二尖瓣瓣膜病

风湿性心脏病是A组链球菌感染反复发作后遗留的轻重程度不同的心脏疾病, 最常见受累部位是二尖瓣瓣膜, 目前已有研究表明瓣膜退变与炎症的严重程度相关^[20]。Demir等^[21]对368例二尖瓣狭窄(rheumatic mitral valve stenosis, RMVS)患者和80例健康受试者进行研究, 发现CRP和MHR显著增加与二尖瓣狭窄的严重程度平行, Spearman相关分析表明CRP与MHR之间存在显著正相关, 提示MHR可用于预测RMVS的严重程度。二尖瓣脱垂(mitral valve prolapse, MVP)是一种常见的疾病, 占总人口的2%~3%, 二尖瓣脱垂与心律不齐以及动脉粥样硬化导致的心脏猝死之间存在关联。Abacioglu等^[22]对82例MVP患者和78例正常人进行研究, 发现MVP患者的MHR值较高。MVP组单核细胞计数和MHR明显高于对照组, MHR值与返流面积成正比。提示MHR与MVP和返流面积密切相关, 可考虑作为MVP患者的预后指标。

6 MHR与心肌病

肥厚型心肌病(hypertrophic cardiomyopathy, HCM)是最常见的遗传性心肌病之一, 这种疾病影响所有年龄组, 具有显著的临床异质性, 不良的临床结果有严重限制性症状、晚期心力衰竭、全身栓塞事件、脑卒中、恶性心律失常事件, 甚至心脏死亡。近几十年来, 炎症和氧化应激在HCM发病机制和预后判断中的作用受到广泛关注。Ekizler等^[23]对411例肥厚型心肌病患者进行研究, 主要终点是心血管死亡或恶性心律失常事件, 结果显示: 54例(13.1%)患者出现了主要终点, ROC分析显示以14.57为临界值, MHR预测主要终点发生的敏感性和特异性分别为72%和72%。在多变量模型中, 高MHR是主要终点的唯一有意义的预测因子。提示高MHR水平可能是HCM患者恶性

心律失常和死亡的独立预测因子。围产期心肌病(peripartum cardiomyopathy, PPCM)是一种罕见严重威胁生命的妊娠并发症,患者常在妊娠末期或产后头几个月发生不明原因的心力衰竭,EF通常<45%。导致PPCM的确切病理生理机制尚不清楚,但遗传基础、病毒性心肌炎、对妊娠的异常免疫或血流动力学反应、营养缺乏、氧化应激增加和炎症都和其发生有关。Ekizler等^[24]对64例患有持续性左心室收缩功能不全(left ventricular systolic dysfunction, LVSD)的PPCM患者随访至少12个月,恢复标准为左室射血分数>45%,结果显示:35名(55%)在最后2次随访时有持续性LVSD,29名(45%)表现出左室射血分数改善;未恢复组MHR水平明显高于恢复组。在单因素分析中,MHR水平升高显著预示左心室不能恢复。以9.73作为临界值,MHR预测持续性左心室收缩功能障碍的敏感性为89%,特异性为79%。提示MHR升高是PPCM患者持续左心室收缩功能不全的重要预测因子。MHR可能有助于确定PPCM的高危患者。

7 MHR 与心房颤动

心房颤动(atrial fibrillation, AF)是CVD中最常见和最复杂的心律失常之一,与高致残率和高病死率有关。其发病机制较为复杂,而纤维化和炎症的生物标志物是AF心房重构的重要病理生理因素。炎症在AF的发生、持续和复发中具有重要的作用,Kume等^[25]通过大鼠实验发现单核细胞可能参与了AF心房重构的发展。Shahid等^[26]对AF患者的血样进行单核细胞计数,发现高单核细胞数与AF患者的不良血栓形成和出血存在关系。Shahid等^[27]报道单核细胞触发炎症级联反应,最终会导致纤维化,预防心房纤维化可以延缓AF的发展。Zhang等^[28]研究发现单核细胞趋化蛋白-1诱导蛋白(monocyte chemotactic protein-1 inducible protein, MCP1P)在老年AF患者中的表达最高,MCP1P在年龄相关性AF患者中的表达高于其他患者组,并与AF诱导的纤维化有关。Suehiro等^[29]曾在AF消融手术过程开始中进行心房电压标测,发现有低电压区(low-voltage zones, LVZs)的患者中间单核细胞比例明显高于无LVZs的患者。TLR4在中间单核细胞中的表达频率明显高于其他2个单核细胞亚群。此外,中间单核细胞中TLR4的表达水平与LVZs总面积呈正相关,尤其是阵发性AF患者的中间单核细胞和TLR4的表达与LVZs呈正相关。Pfluecke等^[30]对73例接受了肺静脉隔离(pulmonary vein isolation,

PVI)治疗的症状性AF患者随访分析,发现AF复发组($n=20$)单核细胞-血小板聚集物(monocytes-platelet aggregates, MPAs)含量升高,单核细胞CD41 mRNA表达增加。MPAs可以作为成功PVI的标志物或作为停止抗凝剂治疗的辅助决策。高密度脂蛋白(high-density lipoprotein, HDL)具有抗炎、抗氧化和抗血栓的特性。因此高密度脂蛋白的功能损害可能与AF的启动或进展有关。Trieb等^[31]对AF患者导管消融术前与术后HDL质量学指标研究,发现AF患者的高密度脂蛋白胆固醇流出能力、高密度脂蛋白颗粒数、载脂蛋白A-I水平和脂酰基转移酶活性均显著低于健康人,在窦性心律恢复后,胆固醇流出能力、高密度脂蛋白颗粒数、载脂蛋白A-I水平以及脂蛋白过氧化氢酶活性均恢复。高密度脂蛋白颗粒的数量和功能可作为AF发生和进展的替代标志物,并有助于识别高危患者。Okin等^[32]对8 267例无AF病史的高血压患者随访研究,提示低HDL治疗与新AF的风险密切相关,未来的研究可能会调查增加高密度脂蛋白的疗法是否可以降低发生AF的风险。一项荟萃分析^[33]显示HDL-C水平升高与AF风险降低相关,HDL-C水平与AF风险呈反比关系。Boudi等^[34]收集6 881名非STEMI患者入院后24 h的空腹血脂谱,在首次出现心律失常后,对患者进行了长达6年的随访,结果发现低高密度脂蛋白水平与AF和其他心律失常的发展之间存在显著关联。氧化应激似乎与AF的发病和持续有关。Ulus等^[35]研究显示:MHR是老年ACS患者PCI术后新发AF的独立预测因子。Saskin等^[36]回顾性分析662例术前窦性心律行单纯冠状动脉旁路移植术(coronary artery bypass grafting, CABG)患者,logistic回归分析发现术前单核细胞计数/高密度脂蛋白胆固醇比值是术后AF(postoperative atrial fibrillation, POAF)的预测因子。术前单核细胞计数/高密度脂蛋白胆固醇比值也是术后早期病死率的预测因素。Tekkesin等^[37]对311例CABG患者进行研究,发现71例出现POAF。POAF(+)组的M/H比值明显高于POAF(-)组,提示M/H比值在AF的发病中起重要作用。Satilmis^[38]对203例病态窦房结综合征患者植入双起搏器(dual-chamber pacemaker, DDDR)后随访,在DDDR植入术后6个月的临床随访中,51例(25.1%)患者至少有1次心房高频率发作。多元Cox回归分析发现M/H比值与DDDR患者心房高频率发作有关。MHR是双起搏器植入术后发生无症状性AF的独立预测因子。但目前国内外关于MHR与AF的研究报道较少,还需要进一步的临床研究提供可靠依据。

8 结语

综上所述, MHR值水平升高在CVD的发生、发展和预后中有重要的预测和预后价值, 是一种实用、经济、便捷、高预测性的新型心血管病标志物。在临床实践中, MHR的简单计算是使用该指标预测疾病的优点之一。但在早期临床干预的具体节点仍不明确, 期待有更大规模关于MHR与CVD的临床研究, 为评估CVD的预后、早期干预可能发生的不良心血管事件提供可靠依据。

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