

综述

心肌内出血与心肌梗死后不良心室重构的关系研究进展

陈润都^{1,2}, 张颖倩¹, 佟伟¹, 李力兵³, 吴远斌^{2,3}, 周昊^{1,2}, 陈韵岱^{1*}¹解放军总医院心血管病医学部, 北京 100853; ²解放军医学院研究生院, 北京 100853; ³解放军总医院第一医学中心心脏大血管外科, 北京 100853

[中图分类号] R541.4

[文献标志码] A

[DOI]

10.11855/j.issn.0577-7402.2022.02.0186

[声明]

本文所有作者声明无利益冲突

[引用本文]

陈润都, 张颖倩, 佟伟, 等. 心肌内出血与心肌梗死后不良心室重构的关系研究进展[J]. 解放军医学杂志, 2022, 47(2): 186-191.

[收稿日期] 2021-09-06

[录用日期] 2021-09-29

[上线日期] 2022-01-07

[摘要] 心肌梗死是由心肌缺血缺氧引起的心肌细胞坏死, 是全球范围内死亡和致残的重要原因。直接经皮冠状动脉介入治疗虽然可恢复心外膜冠脉血流, 降低心肌梗死的病死率, 但是部分心肌梗死患者仍会发展为慢性心力衰竭。心肌内出血(IMH)为严重微血管损伤引起的红细胞外渗, 是再灌注治疗引起的重要并发症, 可作为心肌梗死后不良心室重构的独立预测因子, 而不良重构是心肌梗死后心力衰竭发生的病理基础。目前IMH的评价方式主要为心脏磁共振技术, 尤其是可利用T₂*序列实现对IMH的定性和定量评估。有研究表明, IMH被降解后留下的铁沉积可加重炎症反应, 导致巨噬细胞聚集, 分泌基质金属蛋白酶, 而后者参与了随后的不良心室重构过程。本文针对近年来关于IMH与心肌梗死后不良心室重构关系的临床和基础研究进展进行综述, 旨在为心肌内出血的防治提供参考。

[关键词] 心肌内出血; 缺血再灌注损伤; 不良心室重构

Relationship between intramyocardial hemorrhage and adverse ventricular remodeling after myocardial infarction

Chen Run-Du^{1,2}, Zhang Ying-Qian¹, Tong Wei¹, Li Li-Bing³, Wu Yuan-Bin^{2,3}, Zhou Hao^{1,2}, Chen Yun-Dai^{1*}¹Department of Cardiovascular Medicine, Chinese PLA General Hospital, Beijing 100853, China²Graduate School of Chinese PLA Medical College, Beijing 100853, China³Department of Cardiac and Vascular Surgery, the First Medical Center of Chinese PLA General Hospital, Beijing 100853, China

*Corresponding author, E-mail: cyundai@vip.163.com

This work was supported by the National Natural Science Foundation for Distinguished Young Scholars (81800221), and the National Major Scientific Equipment and Instruments Development Project (81827808)

[Abstract] Myocardial infarction (MI) is cardiomyocyte necrosis caused by myocardial ischemia and hypoxia, and is the leading cause of death and disability in the world. Although direct percutaneous coronary intervention (PCI) can restore epicardial coronary blood flow and reduce the mortality of MI, some patients with MI will still develop into chronic heart failure. As an important complication caused by reperfusion therapy, intramyocardial hemorrhage (IMH) is defined as red blood cell extravasation caused by severe microvascular injury, and can be used as an independent predictor of the adverse ventricular remodeling after myocardial infarction, which is the pathological basis of heart failure after myocardial infarction. At present, the main evaluation method for IMH is cardiac magnetic resonance imaging (MRI), especially the qualitative and quantitative evaluation of intracardial bleeding can be achieved by T₂* sequence. It has been shown that iron deposition after degradation of IMH exacerbates the inflammatory response, leading to the aggregation of macrophages and secretion of matrix metalloproteinases, which are involved in subsequent adverse ventricular remodeling. The recent progress of clinical and basic research on the relationship between IMH and the adverse ventricular remodeling after MI are reviewed in present paper, hoping to be helpful for the prevention and treatment of

[基金项目] 国家自然科学基金青年科学基金项目(81800221); 国家重大科研仪器研制项目(81827808)

[作者简介] 陈润都, 博士研究生, 主要从事心肌缺血再灌注损伤方面的研究

[通信作者] 陈韵岱, E-mail: cyundai@vip.163.com

IMH in the future.

[Key words] intramyocardial hemorrhage; ischemia reperfusion injury; adverse ventricular remodeling

直接经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)是ST段抬高型心肌梗死(ST segment elevation myocardial infarction, STEMI)的重要治疗方法^[1]。PCI可显著降低心肌梗死的病死率,延长患者寿命^[2],但心肌梗死后的心力衰竭发生率仍较高,术后5年心力衰竭的发生率可达21.8%^[3]。部分STEMI患者虽然心外膜下血管成功实现了再灌注,但却存在微血管损伤,也称为无复流现象,在很大程度上抵消了早期干预的疗效。微血管损伤主要包括微血管阻塞(microvascular obstruction, MVO)和心肌内出血(intramyocardial hemorrhage, IMH),其中IMH为微血管损伤引起的红细胞外渗^[4],而IMH的出现也提示微血管损伤的程度较为严重^[5]。不良室重构(adverse ventricular remodeling, AVR)为机体在受损心肌负荷过重的情况下做出的反应,包括结构和功能两方面的异常,是急性心肌梗死(acute myocardial infarction, AMI)后心力衰竭的病理基础^[6]。Tennant等^[7]在20世纪30年代首先描述了AVR,包括心室扩张、瘢痕形成和整个左心室形态的几何变化(从椭圆形到球形)。本文对近年来关于IMH与心肌梗死后AVR关系的临床和基础研究进展进行综述,旨在为IMH的防治提供参考。

1 IMH与AVR的关系

1.1 IMH预测AVR的临床研究

在心肌缺血再灌注(I/R)损伤后,渗入心肌组织的红细胞逐步被降解成氧化血红蛋白、脱氧血红蛋白、高铁血红蛋白,数周后随着巨噬细胞的吞噬,最终变成铁蛋白和含铁血黄素,产生顺磁效应,使IMH能被磁共振成像(MRI)检测到。Husser等^[8]使用心血管磁共振成像(cardiovascular magnetic resonance, CMR) T_2^* 序列证实,IMH是再灌注后AVR发生的独立预测因子,在急性期与更低的左心室射血分数(left ventricular ejection fraction, LVEF)、更大的梗死面积、更低的收缩期心室壁厚度相关,而在慢性期则与更差的LVEF恢复和AVR独立相关。此外,IMH也与主要心脏不良事件(major adverse cardiac events, MACE)的发生率相关。 T_2^* 序列对含铁代谢物产生的顺磁效应较为敏感,被认为是最适合检测IMH的核磁序列^[9]。Ferré-Vallverdú等^[10]使用 T_2^* 序列进一步确定了IMH与MVO、MACE的关系。

目前,使用MRI对IMH进行定量分析的研究较少。Carrick等^[11]分别采用 T_2^* 序列和钆对比剂

延迟强化磁共振成像(late gadolinium enhancement-magnetic resonance imaging, LGE-MRI)对IMH和MVO进行定量分析,并比较了两者的变化趋势,发现出血性心肌梗死患者的MVO程度在再灌注后4~12h即加重,第3天时维持不变,于第10天时明显缓解;而出血量在4~12h逐渐增多,第2天达峰,于第10天时下降,但由于该研究的影像仅分析了3个短轴切面,因此可能遗漏轻微出血。Amier等^[12]采用CMR检测IMH并进行定量分析,根据IMH的中位数将患者分为无IMH、轻度IMH和广泛IMH,发现广泛IMH组无论是梗死面积还是心功能方面[LVEF、左心室收缩末期容积(LVESV)、左心室舒张末期容积(LVEDV)等]均较轻度IMH组差,而轻度IMH组的上述指标较无IMH组差,提示IMH出血量与AVR程度呈正相关。但是,目前认为最适合用于检测IMH的手段是 T_2^* 序列^[9],而Amier等^[12]的研究却采用了CMR- T_2^* 序列,在一定程度上可能影响了其结果的应用价值。

1.2 IMH造成的铁沉积致AVR的机制

IMH发生后,渗入受损心肌的红细胞逐步被降解,最终变成铁蛋白和含铁血黄素,形成铁沉积^[13]。通过扫描透射电子显微镜和能量色散X射线荧光光谱分析,研究者发现慢性铁沉积实际上是以直径 $>1\ \mu\text{m}$ 的纳米晶体(分子式为 $\text{Fe}_2\text{O}_3 \cdot 0.5\text{H}_2\text{O}$)形式包裹在巨噬细胞的膜结构中,类似于溶酶体^[14]。这些研究结果表明,慢性心肌梗死区域内的铁沉积实际上是由纳米晶铁组成的结节。

体外研究发现,铁孵育的巨噬细胞内核转录因子- κB (NF- κB)被激活,且白细胞介素- 1β (IL- 1β)和肿瘤坏死因子 α (TNF- α)的表达增加,促炎细胞因子表达水平与铁浓度呈正相关^[15]。Cokic等^[16]发现,心肌I/R损伤造成的慢性铁沉积与心肌梗死患者PCI术后的AVR及心律失常有关。Kali等^[14]发现,犬心肌I/R损伤后,CMR可检测到 T_2^* 信号缺失,并将其作为衡量铁沉积容量的指标。此外,他们在病理染色观察时发现,梗死区存在明显的铁沉积和纤维化,且铁沉积的位置与浸润的单核细胞(标志物MAC387)、促炎巨噬细胞(标志物IL- 1β 、TNF- α)、清除血红蛋白的巨噬细胞(标志物CD163)及基质金属蛋白酶-9(MMP-9)的位置是重合的,炎性细胞因子含量与铁负荷呈正相关^[14]。IL- 1β 、TNF- α 在心肌梗死后心室体积扩大、心脏收缩功能受损的过程中起关键作用。巨噬细胞释放的促炎细胞因子在很大程度上促进了MMP的活化及AVR和心功

能障碍的发生^[17],而MMP-9的活性与细胞外基质(extracellular matrix, ECM)降解和瘢痕组织机械结构的改变有关^[18]。因此,IMH导致的铁沉积可促进单核细胞向I/R损伤心肌浸润,并调节巨噬细胞亚型及ECM。

单克隆抗体Mac387可识别3种钙粒蛋白(钙结合蛋白),这些蛋白均存在于新招募的单核细胞中,但随着单核细胞向巨噬细胞分化,Mac387的免疫反应性明显降低,可作为心脏的炎症反应指标。Mac387阳性细胞在心肌I/R损伤后1 h内广泛浸润梗死区,但在心肌I/R损伤7 d后则很少。Kali等^[19]发现,IMH后的慢性铁沉积加重并延长了炎症反应的持续时间,而Mac387阳性细胞在慢性铁沉积区的选择性募集可能是IMH致AVR的潜在机制之一。此外,有研究发现,铁沉积可导致来源于Mac387阳性单核细胞的浸润巨噬细胞处于一种促炎状态,它们吞噬血红蛋白降解产物后在胞内形成铁超载,使炎症反应持续存在,进而加重AVR的程度,这可解释心肌I/R损伤后IMH造成的铁沉积与AVR及心力衰竭之间的相关性^[20]。

在IMH时,铁大量积聚在心肌梗死的核心区域内,这也是巨噬细胞大量聚集的部位^[21]。从机制上讲,及时抑制铁沉积导致的炎症反应可缓解心肌梗死后的AVR^[22],而长时间的炎症反应可阻碍胶原沉积和瘢痕形成,导致抗拉强度降低和左心室扩张。有研究发现,心肌梗死后对炎症的有效抑制可缓解AVR^[23]。铁沉积有可能成为梗死后心力衰竭的治疗靶点。Kali等^[14]发现,心肌梗死患者给予3个月以上的细胞内铁螯合物治疗可降低AVR的发生率。这在后来猪的心肌I/R损伤模型中得到证实,铁螯合物可有效减轻AVR的程度^[24]。但Kali等^[14]的研究并未发现功能性AVR参数(如LVEDV、LVESV和LVEF)与铁容量存在明显的相关性,这可能与其样本量较小有关。Tanner等^[25]发现,与标准的去铁胺螯合疗法相比,联合应用去铁酮可明显降低轻、中度心脏铁负荷的地中海贫血患者的心肌铁含量,改善射血分数和内皮功能。

2 单核-巨噬细胞与AVR

心肌梗死后,受损心肌内部的巨噬细胞分为趋化因子受体2(CCR2)阴性的常驻巨噬细胞和CCR2阳性的非常驻巨噬细胞。常驻巨噬细胞起源于卵黄囊或胎肝,占有非心肌细胞的7%~8%,具有免疫监视和调节心脏功能的作用,但在心肌梗死后会迅速耗尽^[26]。此时,循环中的单核细胞将被招募至心肌,分化为CCR2阳性的非常驻巨噬细胞,参与疾病的发展进程。被动员的单核细胞一方面来自外周

血,另一方面来自于脾储库^[27],这些单核细胞分化为非常驻巨噬细胞后,可吸引中性粒细胞至受损心肌,进一步加重炎症反应^[28]。

2.1 单核细胞的亚型及与AVR的关系 人经典单核细胞表型为CD14⁺⁺CD16⁻,而小鼠的经典单核细胞表型为Ly-6C^{high}。在人体内,经典单核细胞约占所有循环单核细胞的90%,由于经典单核细胞的标志物CD62和CCR2呈现高表达的特点,因此可被募集至MCP-1、趋化因子CCL2和CCL7高表达的部位^[29]。小鼠Ly-6C^{high}单核细胞在心肌梗死后第3天达峰值,可产生炎性细胞因子和一氧化氮,并分化为巨噬细胞和树突状细胞,参与坏死心肌的分解^[30]。Tsujioka等^[31]发现,在人体内,经典单核细胞的峰值水平与心肌梗死6个月后的LVEF水平和心肌挽救指数(myocardial salvage index, MSI)呈负相关。以上研究均提示AMI后经典单核细胞可被募集至受损心肌,促进AVR的发生。

人非经典单核细胞的表型为CD14⁺CD16⁺,小鼠非经典单核细胞为Ly-6C^{low}。在人体内,趋化因子fractalkine及其受体CX3CR1可将CD14⁺CD16⁺细胞募集至梗死部位^[32]。非经典单核细胞主要以一种稳定的形式存在于血管壁,主要功能为清除氧化脂质、细胞碎片和病原体等^[27]。非经典单核细胞对急性心肌梗死的炎症过程至关重要。转录因子NR4A1(又称Nur77)在小鼠经典单核细胞向非经典亚群的再分化过程中起重要作用^[33]。有研究发现,小鼠Ly-6C^{low}细胞数量在心肌梗死后第5天达到高峰,可通过分泌VEGF和TGF- β 调节瘢痕形成、血管生成及心肌愈合过程^[34],且心肌梗死后募集到梗死部位的非经典单核细胞数量与LVEF呈正相关^[35]。但就整个梗死过程而言,经典单核细胞在数量上仍然占据优势^[30]。在小鼠中还存在着一种与炎症相关的中间单核细胞(CD14⁺⁺CD16⁺),是经典单核细胞与非经典单核细胞之间的一种过渡形态^[30]。总之,非经典单核细胞被趋化因子fractalkine募集到梗死部位后,可通过调节瘢痕形成、血管生成及炎症反应起到抑制AVR的作用。

2.2 巨噬细胞的亚型及与AVR的关系 巨噬细胞具有双重作用:一方面可清除组织中的坏死残留物,另一方面可分泌促分解介质^[36]。与单核细胞相似,巨噬细胞的不同亚群也参与了不同的炎症反应过程。巨噬细胞分为M1型和M2型两种亚群,粒-巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor, GM-CSF)可使单核细胞向M1型分化,发挥促炎作用,而巨噬细胞集落刺激因子(macrophage colony-stimulating factor, M-CSF)可使单核细胞向M2型分化,发挥抑制炎症、修复组织

的作用。目前在体外实验中诱导巨噬细胞分化的方法比较成熟,可分别使用 γ 干扰素(IFN- γ)或IL-4使巨噬细胞向M1或M2型转变^[37]。

M1型巨噬细胞具有促炎作用,可产生IL-1 β 、IL-6和TNF- α 等细胞因子。阻断M1极化通路可使小鼠冠状动脉结扎后3周的左心室扩张情况得到明显改善^[38],且小鼠M2型巨噬细胞表型CD206表达上调^[39]。有研究发现,在人心肌梗死后的再生期(第4~10天),受损心肌内的巨噬细胞可达到峰值,且在10 d后维持在较高水平^[40]。M2型巨噬细胞具有抗炎作用,可激活成纤维细胞,诱导细胞增殖、胶原沉积和血管生成^[41]。M2型巨噬细胞可再细分为M2a、M2b和M2c三种亚型,其中M2a和M2c巨噬细胞主要与特异性免疫细胞即T细胞、B细胞、NK细胞合作,发挥促进组织修复和抗炎的作用,而M2b细胞可在IL-1等刺激因素的影响下产生抗炎和促炎细胞因子(如IL-10、IL-1 β 、IL-6)^[42],在心肌损伤后的抗凋亡和抗纤维化中发挥重要作用。浸润至受损心肌的M2b巨噬细胞可上调心肌细胞中锌指蛋白A20的表达,抑制NF- κ B的活性,进而抑制炎症反应和细胞凋亡^[43]。M2b细胞还能通过抑制丝裂原活化蛋白激酶信号通路发挥抗纤维化的作用,从而抑制心肌I/R损伤后的AVR^[44]。在心肌缺血时,通过移植或其他方式激活M2b巨噬细胞,可能是减轻心肌I/R损伤的一种新方法^[43]。

然而,巨噬细胞M1/M2极化分型及其对AVR的作用目前仍存在争议。Yang等^[45]敲除小鼠GATA3(一种参与M2表型分化的转录因子)后,发现心肌组织中CCR2⁺/Ly-6C^{high}巨噬细胞的存在时间明显延长,但与野生型小鼠相比,GATA3^{-/-}小鼠在2个月的观察中表现出了左室功能改善,因此质疑Ly-6C^{high}即经典单核细胞在心脏重塑中的有害作用。Zlatanova等^[46]发现,在M1型极化和炎症状态下,缺乏铁调素的巨噬细胞也显示出促修复的能力。因此,巨噬细胞应根据其功能来进行定义,而非简单地根据M1/M2分型来推测其功能。

通过沉默CCR2减少巨噬细胞浸润可能对心肌I/R损伤发挥保护作用。已有研究发现,敲除CCR2可降低转化生长因子 α (TGF- α)、IL-1 β 、MMP-9、基质金属蛋白酶组织抑制因子1(TIMP-1)的表达水平,并减轻I/R损伤^[47]。还有研究发现,沉默CCR2可使apoE^{-/-}小鼠冠状动脉结扎术后第4天梗死区内的Ly-6C^{high}单核细胞减少41%,并可减小再灌注后3 d的梗死范围,降低再灌注后7 d的心肌纤维化程度,也使3周后的AVR得到明显改善^[48]。此外,沉默CCR2可使心肌梗死后第21天的射血分数从29%提高到35%,但其他指标如新生血管数量和瘢痕组织中

的I型胶原含量未受到明显影响,提示沉默CCR2后的心功能改善与内皮细胞和成纤维细胞无直接关系^[49]。

Patel等^[50]对小鼠行主动脉弓缩窄术(transverse aortic constriction, TAC)发现,CCR2⁺巨噬细胞在压力超负荷导致的心肌肥大和心力衰竭中起着重要作用,在发生心室增大和持续性左室收缩功能障碍之前,循环中Ly-6C^{high}-CCR2⁺单核细胞即明显增多,这对心脏的早期代偿性肥大,抗原提呈,CD4⁺、CD8⁺ T淋巴细胞活化具有重要作用;但随后,CD4⁺ T淋巴细胞与CCR2⁺巨噬细胞共同产生组织损伤反应,最终导致病理性肥大、间质纤维化和左心室收缩功能障碍。如在压力超负荷早期(术后3~7 d)使用RS504393对CCR2信号进行阻断,可减轻AVR、收缩功能障碍和心脏纤维化^[51]。在慢性心力衰竭期,抑制CCR2⁺巨噬细胞浸润也可阻止T淋巴细胞浸润^[49]。以上研究结果提示,单核细胞衍生的CCR2⁺心肌巨噬细胞是心肌梗死发展和随后向心力衰竭过渡所必需的,也是防止AVR的关键点。

3 MMP-9在IMH和AVR中的作用

3.1 MMP-9与IMH 再灌注后,心肌梗死患者的心肌组织内MMP活性上调。MMP尤其是MMP-9可破坏血管基底膜,使血液外渗而形成IMH。在大鼠脑梗死模型中,抑制MMP-9可降低出血风险^[52]。MMP-9的抑制可通过在再灌注前耗尽白细胞或使用MMP-9抑制剂(如阿托伐他汀、依达拉奉、褪黑素、米诺环素和利莫那班)来实现,且在再灌注早期给药时其抑制作用最为明显^[4],但仍需更多的研究加以验证。

3.2 MMP-9与AVR MMP是调节ECM反应的关键蛋白酶家族,而ECM是AVR的关键因子。ECM底物包括胶原蛋白、弹性蛋白、纤维连接蛋白、半乳糖凝集素-3、层黏连蛋白、pro-MMP-2、pro-MMP-13和卵黄连蛋白。非ECM底物主要包括IL-1 β 、IL-8、血小板因子4、内皮素-1和 α_2 -巨球蛋白^[53]。在心肌梗死早期MMP-9即增加,而敲除MMP-9基因可抑制AVR并改善预后^[54]。人血浆MMP-9水平可预测心血管疾病的死亡发生率,基线时的MMP-9水平与随访4年的心血管疾病病死率呈正相关^[55]。血浆MMP-9和TIMP-1与舒张末期容积增加相关,是AVR和不良预后的临床生物标志物^[55]。心肌成纤维细胞参与了心肌梗死后的心肌重塑,在梗死区分泌胶原蛋白和其他ECM成分组成替代性瘢痕组织,同时也在非梗死区域产生纤维化^[56]。敲除MMP-9可减弱I型胶原和III型胶原表达上调的趋势,从而抑制成纤维细胞介导的AVR^[56]。

4 总结与展望

IMH为心肌梗死后较为严重的微血管损伤,预后较差,目前已成为广受关注的临床现象。CMR尤其是T₂*序列对于IMH的诊断和定量具有重要作用,但定量研究IMH与AVR关系的临床研究仍较少。巨噬细胞不仅是心肌组织中的关键成分,也是AVR的关键细胞类型,因此,靶向巨噬细胞在减轻心肌I/R损伤和心肌梗死后AVR方面有着良好的应用前景。随着对巨噬细胞认识的加深,未来可针对巨噬细胞亚型和特定信号模式,观察巨噬细胞如何协调心肌修复,从而协助确定新的干预靶点,为临床提供新的治疗策略。对于IMH、巨噬细胞及AVR之间的具体关系,以及相关的干预措施值得深入探讨。

【参考文献】

- [1] Ibanez B, James S, Agewall S. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC) [J]. *Eur Heart J*, 2018, 39(2): 119-177.
- [2] Cheng B, Gao LY. Effect of early intervene in non-culprit vessels on the prognosis of patients with acute ST-segment elevation myocardial infarction presenting with multivessel disease[J]. *Med J Chin PLA*, 2020, 45(4): 441-446. [成彪,高凌云.早期干预非罪犯血管对急性ST段抬高型心肌梗死合并多支血管病变患者预后的影响[J].解放军医学杂志,2020,45(4):441-446.]
- [3] Torabi A, Cleland JG, Khan NK, et al. The timing of development and subsequent clinical course of heart failure after a myocardial infarction[J]. *Eur Heart J*, 2008, 29(7): 859-870.
- [4] Betgem RP, de Waard GA, Nijveldt R, et al. Intramyocardial haemorrhage after acute myocardial infarction[J]. *Nat Rev Cardiol*, 2015, 12(3): 156-167.
- [5] Liu DY, Cao F. Advances in intramyocardial hemorrhage of perfused acute myocardial infarction by cardiovascular magnetic resonance[J]. *Med J Chin PLA*, 2020, 45(8): 857-861. [刘冬月,曹丰.磁共振评估心肌梗死再灌注后心肌内出血的研究进展[J].解放军医学杂志,2020,45(8):857-861.]
- [6] van der Bijl P, Abou R, Goedemans L, et al. Left ventricular post-infarct remodeling[J]. *JACC Heart Fail*, 2020, 8(2): 131-140.
- [7] Tennant R, Wiggers CJ. The effect of coronary occlusion on myocardial contraction[J]. *Am J Physiol Leg Content*, 1935, 112(2): 351-361.
- [8] Husser O, Monmeneu JV, Sanchis J, et al. Cardiovascular magnetic resonance-derived intramyocardial hemorrhage after STEMI: Influence on long-term prognosis, adverse left ventricular remodeling and relationship with microvascular obstruction[J]. *Int J Cardiol*, 2013, 167(5): 2047-2054.
- [9] Demirkiran A, Everaars H, Amier RP, et al. Cardiovascular magnetic resonance techniques for tissue characterization after acute myocardial injury[J]. *Eur Heart J Cardiovasc Imaging*, 2019, 20(7): 723-734.
- [10] Ferré-Vallverdú M, Sánchez-Lacuesta E, Plaza-López D, et al. Prognostic value and clinical predictors of intramyocardial hemorrhage measured by CMR T2* sequences in STEMI[J]. *Int J Cardiovasc Imaging*, 2021, 37(5): 1735-1744.
- [11] Carrick D, Haig C, Ahmed N, et al. Myocardial hemorrhage after acute reperfused ST-segment-elevation myocardial infarction: relation to microvascular obstruction and prognostic significance[J]. *Circ Cardiovasc Imaging*, 2016, 9(1): e004148.
- [12] Amier RP, Tijssen RYG, Teunissen PFA, et al. Predictors of intramyocardial hemorrhage after reperfused ST-segment elevation myocardial infarction[J]. *J Am Heart Assoc*, 2017, 6(8): e005651.
- [13] Li L, Liang YB, Chen L, et al. Effects of different preparation methods of nuclear solid red dye on hemosiderin staining[J]. *Chin J Clin Exp Pathol*, 2020, 36(7): 861-863. [李莉,梁永波,陈玲,等.核固红染液不同配制方法对含铁血黄素染色的影响[J].临床与实验病理学杂志,2020,36(7):861-863.]
- [14] Kali A, Cokic I, Tang R, et al. Persistent microvascular obstruction after myocardial infarction culminates in the confluence of ferric iron oxide crystals, proinflammatory burden, and adverse remodeling[J]. *Circ Cardiovasc Imaging*, 2016, 9(11): e004996.
- [15] Scaccabarozzi A, Arosio P, Weiss G, et al. Relationship between TNF-alpha and iron metabolism in differentiating human monocytic THP-1 cells[J]. *Br J Haematol*, 2000, 110(4): 978-984.
- [16] Cokic I, Kali A, Wang X, et al. Iron deposition following chronic myocardial infarction as a substrate for cardiac electrical anomalies: initial findings in a canine model[J]. *PLoS One*, 2013, 8(9): e73193.
- [17] Pilz PM, Hamza O, Gidlöf O, et al. Remote ischemic preconditioning attenuates adverse cardiac remodeling and preserves left ventricular function in a rat model of reperfused myocardial infarction[J]. *Int J Cardiol*, 2019, 285: 72-79.
- [18] Ducharme A, Frantz S, Aikawa M, et al. Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction[J]. *J Clin Invest*, 2000, 106(1): 55-62.
- [19] Kali A, Kumar A, Cokic I, et al. Chronic manifestation of postreperfusion intramyocardial hemorrhage as regional iron deposition[J]. *Circ Cardiovasc Imaging*, 2013, 6(2): 218-228.
- [20] Li JJ, Meng X, Si HP, et al. Hepcidin destabilizes atherosclerotic plaque via overactivating macrophages after erythrophagocytosis[J]. *Arterioscler Thromb Vasc Biol*, 2012, 32(5): 1158-1166.
- [21] Ye YX, Basse-Lüsebrink TC, Arias-Loza PA, et al. Monitoring of monocyte recruitment in reperfused myocardial infarction with intramyocardial hemorrhage and microvascular obstruction by combined fluorine 19 and proton cardiac magnetic resonance imaging[J]. *Circulation*, 2013, 128(17): 1878-1888.
- [22] Frangogiannis NG. Regulation of the inflammatory response in cardiac repair[J]. *Circ Res*, 2012, 110(1): 159-173.
- [23] Dobaczewski M, Xia Y, Bujak M, et al. CCR5 signaling suppresses inflammation and reduces adverse remodeling of the infarcted heart, mediating recruitment of regulatory T cells[J]. *Am J Pathol*, 2010, 176(5): 2177-2187.
- [24] Behrouzi B, Weyers JJ, Qi X, et al. Action of iron chelator on intramyocardial hemorrhage and cardiac remodeling following acute myocardial infarction[J]. *Basic Res Cardiol*, 2020, 115(3):

- 24.
- [25] Tanner MA, Galanello R, Dessi C, *et al.* A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance[J]. *Circulation*, 2007, 115(14): 1876-1884.
- [26] Dick SA, Macklin JA, Nejat S, *et al.* Self-renewing resident cardiac macrophages limit adverse remodeling following myocardial infarction[J]. *Nat Immunol*, 2019, 20(1): 29-39.
- [27] Dutta P, Nahrendorf M. Monocytes in myocardial infarction[J]. *Arterioscler Thromb Vasc Biol*, 2015, 35(5): 1066-1070.
- [28] Li W, Hsiao HM, Higashikubo R, *et al.* Heart-resident CCR2⁺ macrophages promote neutrophil extravasation through TLR9/MyD88/CXCL5 signaling[J]. *JCI Insight*, 2016, 1(12): e87315.
- [29] França CN, Izar MCO, Hortêncio MNS, *et al.* Monocyte subtypes and the CCR2 chemokine receptor in cardiovascular disease[J]. *Clin Sci (Lond)*, 2017, 131(12): 1215-1224.
- [30] Peet C, Ivetic A, Bromage DL, *et al.* Cardiac monocytes and macrophages after myocardial infarction[J]. *Cardiovasc Res*, 2020, 116(6): 1101-1112.
- [31] Tsujioka H, Imanishi T, Ikejima H, *et al.* Impact of heterogeneity of human peripheral blood monocyte subsets on myocardial salvage in patients with primary acute myocardial infarction[J]. *J Am Coll Cardiol*, 2009, 54(2): 130-138.
- [32] Flierl U, Bauersachs J, Schäfer A. Modulation of platelet and monocyte function by the chemokine fractalkine (CX3 CL1) in cardiovascular disease[J]. *Eur J Clin Invest*, 2015, 45(6): 624-633.
- [33] Hilgendorf I, Gerhardt LM, Tan TC, *et al.* Ly-6C^{high} monocytes depend on Nr4a1 to balance both inflammatory and reparative phases in the infarcted myocardium[J]. *Circ Res*, 2014, 114(10): 1611-1622.
- [34] Weinberger T, Schulz C. Myocardial infarction: a critical role of macrophages in cardiac remodeling[J]. *Front Physiol*, 2015, 6: 107.
- [35] Panizzi P, Swirski FK, Figueiredo JL, *et al.* Impaired infarct healing in atherosclerotic mice with Ly-6C(hi) monocytosis[J]. *J Am Coll Cardiol*, 2010, 55(15): 1629-1638.
- [36] Tourki B, Halade G. Leukocyte diversity in resolving and nonresolving mechanisms of cardiac remodeling[J]. *FASEB J*, 2017, 31(10): 4226-4239.
- [37] Murray PJ, Allen JE, Biswas SK, *et al.* Macrophage activation and polarization: nomenclature and experimental guidelines[J]. *Immunity*, 2014, 41(1): 14-20.
- [38] Courties G, Heidt T, Sebas M, *et al.* *In vivo* silencing of the transcription factor IRF5 reprograms the macrophage phenotype and improves infarct healing[J]. *J Am Coll Cardiol*, 2014, 63(15): 1556-1566.
- [39] Shiraishi M, Shintani Y, Shintani Y, *et al.* Alternatively activated macrophages determine repair of the infarcted adult murine heart[J]. *J Clin Invest*, 2016, 126(6): 2151-2166.
- [40] Ryabov V, Gombozhapova A, Rogovskaya Y, *et al.* Cardiac CD68⁺ and stabilin-1⁺ macrophages in wound healing following myocardial infarction: From experiment to clinic[J]. *Immunobiology*, 2018, 223(4-5): 413-421.
- [41] Beyer M, Mallmann MR, Xue J, *et al.* High-resolution transcriptome of human macrophages[J]. *PLoS One*, 2012, 7(9): e45466.
- [42] Gombozhapova A, Rogovskaya Y, Shurupov V, *et al.* Macrophage activation and polarization in post-infarction cardiac remodeling[J]. *J Biomed Sci*, 2017, 24(1): 13.
- [43] Yue Y, Yang X, Feng K, *et al.* M2b macrophages reduce early reperfusion injury after myocardial ischemia in mice: a predominant role of inhibiting apoptosis *via* A20[J]. *Int J Cardiol*, 2017, 245: 228-235.
- [44] Yue Y, Huang S, Wang L, *et al.* M2b macrophages regulate cardiac fibroblast activation and alleviate cardiac fibrosis after reperfusion injury[J]. *Circ J*, 2020, 84(4): 626-635.
- [45] Yang M, Song L, Wang L, *et al.* Deficiency of GATA3-positive macrophages improves cardiac function following myocardial infarction or pressure overload hypertrophy[J]. *J Am Coll Cardiol*, 2018, 72(8): 885-904.
- [46] Zlatanova I, Pinto C, Bonnin P, *et al.* Iron regulator hepcidin impairs macrophage-dependent cardiac repair after injury[J]. *Circulation*, 2019, 139(12): 1530-1547.
- [47] Luster AD. Chemokines--chemotactic cytokines that mediate inflammation[J]. *N Engl J Med*, 1998, 338(7): 436-445.
- [48] Hayasaki T, Kaikita K, Okuma T, *et al.* CC chemokine receptor-2 deficiency attenuates oxidative stress and infarct size caused by myocardial ischemia-reperfusion in mice[J]. *Circ J*, 2006, 70(3): 342-351.
- [49] Patel B, Bansal SS, Ismahil MA, *et al.* CCR2⁺ monocyte-derived infiltrating macrophages are required for adverse cardiac remodeling during pressure overload[J]. *JACC Basic Transl Sci*, 2018, 3(2): 230-244.
- [50] Patel B, Ismahil MA, Hamid T, *et al.* Mononuclear phagocytes are dispensable for cardiac remodeling in established pressure-overload heart failure[J]. *PLoS One*, 2017, 12(1): e0170781.
- [51] Nemska S, Gassmann M, Bang ML, *et al.* Antagonizing the CX3CR1 receptor markedly reduces development of cardiac hypertrophy after transverse aortic constriction in mice[J]. *J Cardiovasc Pharmacol*, 2021, 78(6): 792-801.
- [52] Copin JC, Merlani P, Sugawara T, *et al.* Delayed matrix metalloproteinase inhibition reduces intracerebral hemorrhage after embolic stroke in rats[J]. *Exp Neurol*, 2008, 213(1): 196-201.
- [53] Iyer RP, Patterson NL, Fields GB, *et al.* The history of matrix metalloproteinases: milestones, myths, and misperceptions[J]. *Am J Physiol Heart Circ Physiol*, 2012, 303(8): H919-H930.
- [54] Ramirez TA, Iyer RP, Ghasemi O, *et al.* Aliskiren and valsartan mediate left ventricular remodeling post-myocardial infarction in mice through MMP-9 effects[J]. *J Mol Cell Cardiol*, 2014, 72: 326-335.
- [55] Kelly D, Khan SQ, Thompson M, *et al.* Plasma tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9: novel indicators of left ventricular remodeling and prognosis after acute myocardial infarction[J]. *Eur Heart J*, 2008, 29(17): 2116-2124.
- [56] Mouton AJ, Rivera OJ, Lindsey ML. Myocardial infarction remodeling that progresses to heart failure: a signaling misunderstanding[J]. *Am J Physiol Heart Circ Physiol*, 2018, 315(1): H71-H79.