Advances in Clinical Medicine 临床医学进展, 2023, 13(3), 4616-4622
Published Online March 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.133663

Hans汉斯

铁代谢在心力衰竭中的研究进展

赵　航[1]，吕晋琳[2]

[1]大理大学临床医学院，云南　大理
[2]大理大学第一附属医院，云南　大理

收稿日期：2023年2月21日；录用日期：2023年3月16日；发布日期：2023年3月28日

摘　要

铁是人体必要的微量元素，它对生命体中几乎所有类型的细胞都是必不可少的；铁稳态对人体至关重要，铁的缺乏和过量对人体是有害的，可导致患者发生心力衰竭。因此，必须严格控制铁稳态，以防止缺铁导致贫血以及铁过量使游离铁的产生和活性氧的增加，致组织损伤和器官衰竭。铁调素在调节铁代谢中起着重要的作用，是脊椎动物全身性铁稳态的关键调节剂，当铁调素水平升高时，铁被困在十二指肠肠细胞、肝细胞、脾巨噬细胞及胎盘合胞滋养细胞内，导致血浆铁水平下降。心肌细胞铁调素是自主细胞铁稳态所必需的，心脏铁调素的功能不仅限于调控铁水平，同时也具有抗心肌细胞凋亡、抗心肌肥大和抗心肌纤维化作用。HF患者ID发生率较高，有研究表明对HF患者静脉补充铁剂治疗ID可改善其运动能力和生活质量，连续静脉补铁12周后可减少HF的住院率，口服铁补充剂不能提高运动能力和生活质量，但它们可以减少全因死亡和心力衰竭住院率，但口服铁制剂的胃肠道副作用发生率很高，可能导致胃肠道吸收不良、胃肠道溃疡穿孔、饮食不良或乳糜泻等，此外，铁调素的上调也会减少膳食铁的吸收，因此，目前推荐静脉补充铁剂来治疗HF。

关键词

铁代谢，铁调素，心力衰竭

Research Progress in Iron Metabolism in Heart Failure

Hang Zhao[1], Jinlin Lv[2]

[1]School of Clinical Medicine, Dali University, Dali Yunnan
[2]The First Affiliated Hospital of Dali University, Dali Yunnan

Received: Feb. 21st, 2023; accepted: Mar. 16th, 2023; published: Mar. 28th, 2023

Abstract

Iron is an essential trace element for the human body, it is essential for almost all types of cells in

文章引用: 赵航, 吕晋琳. 铁代谢在心力衰竭中的研究进展[J]. 临床医学进展, 2023, 13(3): 4616-4622.
DOI: 10.12677/acm.2023.133663

the living body. Iron homeostasis is essential for the human body. Iron deficiency and excess are harmful to the human body and can lead to heart failure in patients. Therefore, iron homeostasis must be strictly controlled to prevent anemia due to iron deficiency and the increase of free iron production and reactive oxygen species due to iron overdose, leading to tissue damage and organ failure. Hepcidin plays an important role in regulating iron metabolism and is a key regulator of systemic iron homeostasis in vertebrates. When hepcidin levels are elevated, iron is trapped in duodenal cells, hepatocytes, splenic macrophages, and placental syncytial trophoblasts, resulting in a decrease in plasma iron levels. Cardiomyocyte hepcidin is required for iron homeostasis in autonomous cells, and the function of cardiac hepcidin is not limited to regulating iron levels, but also has the effects of anti-cardiomyocyte apoptosis, anti-myocardial hypertrophy, and anti-myocardial fibrosis. Patients with HF have a higher incidence of ID, studies have shown that intravenous iron treatment with ID improves exercise capacity and quality of life in patients with HF, reduces hospitalization of HF after 12 weeks, oral iron supplementation does not improve exercise capacity and quality of life, but they can reduce all-cause mortality and heart failure hospitalization. However, oral iron preparations have a high incidence of gastrointestinal side effects that may lead to gastrointestinal malabsorption, perforation of gastrointestinal ulcers, poor diet, or celiac disease. In addition, the upregulation of hepcidin also reduces the absorption of dietary iron. Therefore, intravenous iron is currently recommended for HF.

Keywords

Iron Metabolism, Hepcidin, Heart Failure

1. 正常人体的铁代谢及铁调素-铁转运蛋白轴

1.1. 铁的作用

铁(Iron, Fe)是人体必要的微量元素，它对生命体中几乎所有类型的细胞都是必不可少的[1]，Fe 主要由亚铁(Fe^{2+})与氧化铁(Fe^{3+})两种形式参与许多生化反应，是许多细胞代谢途径的重要辅助因子。Fe 参与红细胞中的血红蛋白运输氧气、DNA 合成与代谢、线粒体氧化磷酸化[2] [3]，Fe 的这种化学性质是其参与氧化还原反应的能力的基础[4]，铁稳态对人体至关重要，铁的缺乏和过量对人体是有害的，可导致全身性疾病。有研究表明，长期慢性铁代谢紊乱可能会增加心律失常、心力衰竭、感染、炎症性疾病、糖尿病、肥胖症和非酒精性脂肪性肝病、视网膜退化、肝硬化、癌症、神经退行性疾病和过早死亡的风险[5]，但具体机制尚未完全清楚。因此，必须严格控制铁稳态，以防止缺铁导致贫血，以及铁过量使游离铁的产生和活性氧的增加，致组织损伤和器官衰竭。

1.2. 铁代谢

成人人体含有约 3~5 克铁[6]，理论上 Fe 水平由其吸收和排泄共同决定，其中铁的排泄被认为是一个被动的、不受调节的过程[7]，有研究表明，铁的排泄可能由于肠上皮的更新、失血和死皮脱落[8]，在铁过载时，胆汁中也有少量的 Fe 排泄[7]，但人体中尚未发现已知的铁排泄机制，因此血清铁的水平主要取决于十二指肠吸收铁、巨噬细胞吞噬衰老的红细胞后对铁的回收以及肝脏储存的铁的释放三个方面[9]。其中，十二指肠严格调节铁的吸收对人体铁稳态至关重要，是铁稳态的主要决定因素[10]：食物中的铁(Fe^{3+})

进入人体后，在十二指肠中通过十二指肠细胞色素 b 样蛋白(duodenal cytochrome-b-like protein, DCYTB)转化成 Fe^{2+}，Fe^{2+}再通过二价金属转运体(Divalent metal transporter 1, DMT-1)被肠细胞吸收[11]，通过肠细胞中的 Fe^{2+}可进入线粒体合成血红素，也可以被氧化成 Fe^{3+}储存在铁蛋白中，而过量的铁可通过肠细胞膜上的铁蛋白(ferroportin, FPN)释放到血液循环中，被身体的组织和器官所吸收[12] [13]。

1.3. 铁调素

铁的吸收是一个限速过程，此过程受到铁调素(hepcidin, Hepc)的严格控制。Hepcidin 最初在 2000 年由 Alexander Krause 等人从血液中提取，由于其在肝脏中表达，同时具有抗菌活性，因此被称为肝表达的抗菌肽[14]，后由 C H Park 等人从人类尿液中提取出来[15]，正式命名为铁调素。Hepcidin 由 Hamp 基因(19q13)编码的 84 个氨基酸序列和由碱性氨基酸蛋白水解酶水解的 25 个氨基酸序列紧密折叠而成[16]，含有 4 个二硫键，是一种由肝脏产生并分泌的激素，已被证实是脊椎动物全身性铁稳态的关键调节剂[17]。目前一些研究表明，铁调素不仅可以由肝脏产生，其他器官和组织细胞也可产生少量的铁调素，例如心脏、肺泡巨噬细胞和脾巨噬细胞[18] [19] [20] [21]。

1.4. 铁调素－铁转运蛋白轴

铁调素的产生受血浆铁浓度、肝脏铁储存、红细胞生成活性和炎症的转录调节，并通过与铁转运蛋白(ferroportin, FPN)相结合控制铁的吸收与组织分布[22]，铁调素－铁转运蛋白轴在其中起着重要的作用[23]。而 FPN 是目前已知的唯一的铁输出蛋白[24]，FPN 是一种多膜蛋白，在十二指肠肠细胞、肝 Kupffer 细胞、门静脉周围肝细胞、脾巨噬细胞和胎盘合胞滋养细胞中高度表达[25] [26]。Hepc 与 FPN 结合后，铁转运蛋白经历内化作用和细胞内蛋白水解[9]，导致 FPN 的表达细胞的铁外排受阻。细胞表面铁转运蛋白的损失使得细胞铁向血浆的输送成比例地减少，而其他细胞持续消耗铁会迅速耗尽细胞外铁，导致铁调素诱导的血浆铁浓度降低，导致低铁血症[27]，铁调素的这种诱导低铁血症的作用类似于胰岛素的降血糖作用，当铁调素水平升高时，铁被困在十二指肠肠细胞、肝细胞、脾巨噬细胞及胎盘合胞滋养细胞内[28] [29]，导致血浆铁水平下降。因此，当机体处于缺铁，缺氧，炎症和红细胞合成的状态时，铁调素的表达下降[30]。

2. 铁代谢与心力衰竭

2.1. 心力衰竭

心力衰竭(Heart Failure, HF)是指由于心脏结构或功能的异常导致心室收缩或充盈障碍，而引起的一系列症状和体征的一组综合征[31]。随着全球人口老龄化的加剧，HF 患病率正在逐渐上升，全球估计有 3000 万 HF 患者[32]，有研究表明，仅在美国就有约 570 万的 HF 患者，且每年有 67 万例新发病例[33] [34] [35] [36]，而我国 HF 患者约有 1205 万人，新发患者约 297 万人[37]，由此可见，HF 已经成为世界重要的公共卫生问题之一。

2.2. 铁缺乏与心力衰竭

当机体铁的供应不足以满足身体需求或弥补生理或病理上丢失的铁时，就会出现缺铁(Iron Deficiency, ID)，ID 是全世界最常见的营养缺乏症之一[38]，若 ID 发现的不及时或未予治疗，逐渐会发展为 ID 相关性贫血。心力衰竭患者常合并有 ID，慢性 HF 患者的 ID 患病率为 30%~60% [39]，而急性 HF 患者同样也有很高的患病率，Alain Cohen-Solal 等人对 832 名急性 HF 患者进行了铁水平的分析，其中男性 ID 的患病率为 69%，女性为 75% [40]；ID 被认为是 HF 患者不良结局的预测指标，导致心脏的结构和功能异

常，增加患者死亡率[41]。HF 患者 ID 的机制尚未明确，原因可能由于 1) 营养状况不佳导致铁的摄入减少；2) 静脉淤血导致肠道形态、通透性及吸收性改变，肠道灌注不足，引起肠缺血、水肿及肠道菌群的改变使铁的吸收减少；3) 高龄、多种基础疾病及长期服用阿司匹林等药物导致胃肠道疾病而引起铁的损失增加[42]。目前，全身性铁缺乏的公认标准是血清铁蛋白 <100 μg/L 或血清铁蛋白 100~300 μg 同时转铁蛋白饱和度 < 20% [43]，但炎症和氧化应激可能会使血清铁蛋白水平升高，营养不良可能会降低转铁蛋白饱和度，而铁调素已被认为是识别缺铁的有用生物标志物[44]。

2.3. 铁过载与心力衰竭

铁过载是由于肠道吸收增加、肠外给药或饮食摄入量增加而导致体内过量铁在不同器官中的积累[45]。铁过载最常见的病因是长期输血[46]，当血清铁蛋白水平高于 300 ng/ml 时，表明可能存在铁过载，当血清铁蛋白 >1000 ng/ml 水平可确定铁过载[47]。铁过载时，转铁蛋白饱和，过量的铁与非转铁蛋白结合释放在血液循环中，以 Fe^{2+}的形式通过 L 型钙通道进入心肌细胞，与铁蛋白结合后运输到溶酶体，经过溶酶体降解在心肌细胞长期储存[48]，导致心功能不全，逐渐发展成为心力衰竭。由于铁过载一般常由血液系统疾病引起，如遗传性铁色素沉着症[49]及频繁输血，因此，心脏疾患引起 HF 患者铁过载的研究较少。

2.4. 铁调素与心力衰竭

铁调素作为铁稳态的关键调节剂，在心脏的铁调素表达水平仅次于肝脏[14]。Samira Lakhal-Littleton 等人的研究表明心肌细胞铁调素是自主细胞铁稳态所必需的，心肌细胞中铁调素反应性的减少与心脏铁调素的减少有相同的效果，提示心脏铁调素通过调节心肌细胞 FPN 以自分泌方式起作用。该研究中，将小鼠心肌细胞铁调素进行特异性消融，导致全心铁调素水平大幅降低，小鼠表现出寿命缩短、射血分数降低、收缩功能障碍和心脏肥大[50]。然而，心脏铁调素的功能不仅限于调控铁水平，铁调素在多种 HF 模型中已被证明具有抗心肌细胞凋亡、抗心肌肥大和抗心肌纤维化作用[51] [52] [53]。

3. 补铁治疗与心力衰竭

目前静脉补充铁剂疗已经越来越多地用于治疗心力衰竭中的缺铁，Ziwei Mei 等人的一项关于静脉和口服铁剂治疗心力衰竭患者缺铁的疗效的 meta 分析中表明：对 HF 患者静脉补充铁剂治疗 ID 可改善其运动能力和生活质量，连续静脉补铁 12 周后可减少 HF 的住院率[54]。Raquel López-Vilella 等人的研究中也表明静脉补充铁剂可以改善 HF 合并 ID 患者的射血分数和心脏功能状态[55]。口服铁补充剂不能提高运动能力和生活质量，但它们可以减少全因死亡和心力衰竭住院率[54]，但口服铁制剂的胃肠道副作用发生率很高，可能导致胃肠道吸收不良、胃肠道溃疡穿孔、饮食不良或乳糜泻等，此外，铁调素的上调会减少肠细胞对铁的吸收，同时抑制巨噬细胞铁的释放，因此膳食铁的吸收也会减少[56]，因此，目前推荐静脉铁剂治疗 HF。

4. 展望

目前越来越多的研究探讨铁代谢在心血管疾病中的重要作用，铁调素作为铁代谢的关键调节剂，目前已被认为是识别缺铁的有用生物标志物，铁调素可以早期识别 HF 患者 ID，进而尽早对 HF 患者进行补铁干预治疗，以减少 HF 患者住院率，改善其运动能力及生活质量。但铁调素在铁过载所致的 HF 中的研究仍较少，未来应在这方面多加探索，设计更完善的实验研究以更好地明确铁调素在铁过载所致的 HF 患者中的作用，验证其应用于该领域的应用价值。随着相关研究的增多，相信未来铁调素在 HF 中的作用机制上将有更深入的发现。

基金项目

云南省教育厅科学基金研究项目[2022Y864]。

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