应激性高血糖比与非糖尿病患者急性心肌梗死的相关研究

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【摘要】在危重症状况下,非糖尿病患者出现的暂时性血糖升高,被称为应激性高血糖。相较于单一血糖值,应激性高血糖比调整了上次就餐及基础血糖的影响,有利于非糖尿病急性心肌梗死患者预后的预测。通过对应激性高血糖发生及损伤机制的研究,并进行早期适当治疗,有利于患者预后的改善,值得深入研究。

【关键词】应激性高血糖;应激性高血糖比;急性心肌梗死
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Stress Hyperglycemia Ratio in Non-diabetic Patients with Acute Myocardial Infarction

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【**Abstract**】In critical condition, the temporary elevation of blood glucose in non-diabetics patient is called stress hyperglycemia. Compared with a single blood glucose, stress hyperglycemia ratio adjusted the effects of previous meals and basal glucose, which is helpful to predict the prognosis of non-diabetic patients with acute myocardial infarction. Through the study on the occurrence and injury mechanism of stress hyperglycemia, the prognosis of patients can be improved by appropriate early treatment, and it is worth further research.

【**Key words**】Stress hyperglycemia; Stress hyperglycemia ratio; Acute myocardial infarction

在重大创伤、卒中和败血症等应激状况下,非糖尿病患者因物质及能量代谢紊乱而出现的暂时性血糖升高,被称为应激性高血糖[1]。19 世纪中后期,法国医生 Claude Bernard 发现高血糖与休克患者之间存在关联。到 20 世纪高血糖与急性心肌梗死(acute myocardial infarction AMI)之间的关联逐渐被人们意识到[2]。AMI 是冠状动脉急性、持续性血流减少或中断引起的心肌缺血缺氧,进而出现心肌细胞变性和坏死,是世界各国高死亡率的重要疾病。相关研究显示,在 AMI 患者中,非糖尿病患者较糖尿病患者有着更高的死亡风险[3]。随后的研究也得出相同结论,提示应激性高血糖是 AMI 患者死亡的独立预测因子,尤其对于非糖尿病患者[4-5]。目前的研究多以入院血糖作为应激性高血糖来评估 AMI 患者的预后,但不同患者的基础血糖存在差异,尤其是前次就餐量和就餐时间的差异,可能对结果产生一定的影响。相关研究显示,非糖尿病患者发生 AMI 3 d 后血糖可降至正常水平[6],故以入院第 2 天清晨测得的空腹血糖值作为应激性高血糖,更好地调整了前次就餐的影响,对疾病预后的预测意义更大。Suleiman 等[7]研究发现,入院血糖和第 2 天空腹血糖都是 AMI 患者死亡的独立预测因子,相较于入院时所测的随机血糖值,空腹高血糖对 AMI 患者预后的预测价值更为突出。糖化血红蛋白反映了近 3 ~ 4 个月的平均血糖情况,是反映血糖长期控制的重要指标。研究发现,糖化血红蛋白升高会极大地增加糖尿病和非糖尿病患者心血管疾病的发生风险[8-9]。近年来,另一个反映应激性高血糖的概念被提出,即应激性高血糖比(stress hyperglycemia ratio, SHR),指患者血糖除以平均血糖,平均血糖 = (1.59×糖化血红蛋白) -2.59, SHR = 血糖/[(1.59 × 糖化血红蛋白) -2.59]。SHR 在急性疾病的研究过程中被发现并得以验证,类似体重指数优于体重,SHR 基于基础血糖,故而优于单一血糖值[10-11]。此外,SHR 已被证明是糖尿病和非糖尿病 AMI 患者经皮冠

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脉介入术后反映预后的预测因子[12-15]。SHR 更好地调整了上次就餐及基础血糖的影响,反映了血糖的相对升高程度,因而对疾病预后的预测有着更重要的意义。

流行病学研究显示,无论既往是否合并糖尿病,急性冠脉综合征(ACS)患者都可能出现应激性高血糖,而合并应激性高血糖的患者往往有着更差的预后[16]。Lazaros 等[17]研究发现,非糖尿病 AMI 患者在合并应激性高血糖时,其 1 年内全因死亡、非致死性心肌梗死、心源性休克和再次经皮冠脉介入术的发生率均显著高于其他组,提示应激性高血糖是非糖尿病 AMI 患者发生主要心血管不良事件(MACE)的独立预测因子。Mladenovic 等[18]研究发现,既往无糖尿病的 AMI 患者在合并应激性高血糖时,其 30 d 和 1 年死亡率均较血糖正常组高,而糖尿病 AMI 患者的死亡率与血糖正常组无显著差异,提示非糖尿病 AMI 患者较糖尿病 AMI 患者有着更差的预后。Kim 等[19]研究发现,非糖尿病 AMI 患者在合并应激性高血糖时,其死亡率明显高于糖尿病 AMI 患者。同时,非糖尿病应激性高血糖患者发生心源性休克、脑出血、血红蛋白降低≥5 g/dL、房室传导阻滞和室性心动过速等并发症的概率均高于糖尿病患者。非糖尿病应激性高血糖患者预后往往较糖尿病患者更差,其原因可能是糖尿病患者长期高血糖状态导致心肌细胞对高血糖的慢性适应,因而在血糖急剧变化时表现得不如非糖尿病患者敏感[20]。目前的研究大多以单一血糖值来反映 AMI 患者的应激性高血糖,但不同患者的基础血糖存在较大差异,因而可能存在较大误差。SHR 基于基础血糖,反映血糖的相对升高情况,故能有效地反映患者的应激程度,对糖尿病和非糖尿病 AMI 患者预后的预测均有重要意义。SHR 反映血糖的相对升高程度,故有利于临床工作中鉴别真正的应激性高血糖,指导临床进行早期适当治疗以改善患者预后。

应激性高血糖是 AMI 患者不良预后的重要标志,尤其对于非糖尿病患者,故对非糖尿病 AMI 患者应激性高血糖的机制进行深入探究并进行早期适当治疗显得至关重要。现通过对应激性高血糖发生及损伤机制的阐述,进一步明确应激性高血糖的危害,同时指导临床进行早期适当治疗来改善 AMI 患者的预后。

1 AMI 患者应激性高血糖的发生机制

应激性高血糖是一个复杂的病理生理过程,由生长激素、甲状腺激素、儿茶酚胺类激素、糖皮质激素、胰岛素及胰岛素抵抗和胰高血糖素等共同参与。

1.1 生长激素

AMI 作为一种应激状态,导致垂体生长激素分泌增加,形成受体二聚化而激活酪氨酸激酶 2,激活的酪氨酸激酶 2 与生长激素受体相互磷酸化引起信息分子或信息通道激活而发挥即时效应,包括促进肝细胞糖异生,促进脂肪分解,抑制肌肉糖摄取,产生“抗胰岛素”效应,也可降低外周组织对胰岛素的敏感性,引起血糖升高。

1.2 甲状腺激素

AMI 时,下丘脑-垂体-甲状腺轴的兴奋,甲状腺激素合成及分泌增加,促进小肠黏膜吸收葡萄糖,促进肝糖元分解,抑制肝糖元合成,增强糖异生及糖酵解,使血糖升高。甲状腺激素还能增强胰岛素抵抗并加速胰岛素降解,引起血糖进一步升高。

1.3 儿茶酚胺类激素

AMI 时,蓝斑-交感-肾上腺髓质系统兴奋,释放大量儿茶酚胺类激素,主要为肾上腺素和去甲肾上腺素。肾上腺素激活激酶 A,加速糖原分解,使血糖升高。同时,肾上腺素可激活激素敏感脂肪酶,促进脂肪分解及氧化,引起血糖进一步升高。

1.4 糖皮质激素

AMI 时,下丘脑-垂体-肾上腺皮质轴兴奋,束状带分泌大量糖皮质激素,促进肝糖原异生,减慢葡萄糖氧化,抑制肝外组织对葡萄糖的利用,同时诱导胰岛素抵抗,使血糖升高。同时,糖皮质激素的允许作用,促进儿茶酚胺类激素的作用引起血糖进一步升高。

1.5 胰岛素及胰岛素抵抗

AMI 早期,儿茶酚胺类激素分泌增加引起外周血管收缩,胰腺供血减少,胰岛 B 细胞分泌胰岛素减少,肝外组织对葡萄糖的利用减少, 糖原合成减少,糖异生增加,使血糖升高。随之出现胰岛素抵抗,即高胰岛素血症与高血糖并存[21],其原因可能为胰岛素受体功能异常、组织细胞代谢障碍和炎症介质作用等。

1.6 胰高血糖素

AMI 时,交感神经兴奋引起胰岛 A 细胞胰高血糖素分泌增多,促进肝糖原分解和糖异生,使血糖升高。胰高血糖素又能促进脂肪酸的 β-氧化,增加乙酰辅酶 A 和酮体形成,乙酰辅酶 A 可抑制细胞摄取葡萄糖,抑制糖酵解,进一步升高血糖。

2 AMI 合并应激性高血糖的损伤机制

AMI 合并应激性高血糖往往提示更差的预后,主要由代谢紊乱、内皮功能障碍、氧化应激、炎症反应和高凝状态等多种机制共同参与。

2.1 代谢紊乱

AMI 作为一种应激状态,引起肾上腺髓质分泌大量儿茶酚胺类激素,通过加快心率和增强心肌收缩力,导致舒张期冠状动脉充盈减少及心肌氧耗增加,

加重心肌细胞缺血缺氧,增大梗死面积。同时,肾上腺皮质分泌大量糖皮质激素,促进肝糖元异生,减少机体组织对葡萄糖的利用,脂肪水解为大量的游离脂肪酸,导致线粒体功能障碍,引起心肌细胞膜功能障碍而加重心肌缺血,增加心律失常的发生[22]。游离脂肪酸也可损伤血管收缩功能,并通过增加凝血因子活性而促进血栓形成[23],加重心肌缺血。

2.2　血管内皮功能障碍

高血糖状态可引起血管平滑肌细胞增殖及迁移,促进冠状动脉粥样硬化的发生,导致冠状动脉内皮功能障碍。高血糖状态还可引起一氧化氮和前列环素等释放减少以及超氧化物生成增加[24],进一步加重冠状动脉内皮功能障碍,加重微循环缺血。同时,AMI 时,冠状动脉供血减慢或中断,冠状动脉内皮细胞缺血缺氧严重,引起内皮功能严重紊乱。

2.3　氧化应激反应

高血糖状态可诱发氧化应激反应,引起大量细胞因子如白介素和肿瘤坏死因子等释放,导致血管内皮细胞损伤,进而引起内皮功能障碍,促进动脉硬化的发展,影响心肌细胞血供。Kitano 等[25]研究证明,应激性高血糖会增加患者的氧化应激,从而导致内皮功能障碍并加速动脉粥样硬化,不利于患者预后的发展。

2.4　炎症反应及高凝状态

高血糖状态具有促炎作用,导致机体释放大量炎性介质[26],诱导炎症反应,引起促凝因子大量释放并抑制抗凝物质形成,导致血液黏滞度增加、微循环缺血和心肌缺血缺氧加重。同时,高凝状态使血红蛋白携氧能力下降,导致血氧浓度减低,进一步加重心肌缺血缺氧,导致细胞膜极化障碍,增加心律失常的发生。

3　AMI 患者应激性高血糖的治疗

应激性高血糖与 AMI 患者的预后密切相关,故对合并应激性高血糖的患者进行早期适当治疗有利于其预后的改善。应激性高血糖的治疗方法主要包括口服降糖药物和注射胰岛素,但考虑到 AMI 的危重症病情,目前多推荐胰岛素降糖治疗。胰岛素不但可降低患者血糖,还可拮抗多种炎症因子[27-28]。AMI 患者存在严重代谢紊乱,发生低血糖风险较大,注意动态监测血糖,并及时调整用药剂量。

一项研究显示,胰岛素治疗过程中有发生低血糖可能,一旦发生低血糖,会明显增加患者的死亡率[29]。故目前 AMI 合并应激性高血糖的降糖治疗未达成共识,需进行多重临床试验来验证。

4　总结

AMI 时,非糖尿病患者出现的暂时性血糖升高称为应激性高血糖。应激性高血糖与 AMI 患者的预后密切相关,尤其对于非糖尿病患者。目前的研究大多以单一血糖值来反映应激性高血糖,而相较于单一血糖值,SHR 更好地调整了上次就餐及基础血糖的影响,反映血糖的相对升高程度,有利于患者预后的评估。AMI 合并应激性高血糖的早期识别并适当治疗,有利于患者预后的改善,需更深一步研究。

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