

• 论著 •

容许性低热量喂养与足量喂养对机械通气重症患者预后的影响：一项前瞻性随机对照研究

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【摘要】目的 比较容许性低热量喂养与足量喂养对机械通气(MV)重症患者预后的影响。**方法** 采用前瞻性随机对照研究方法,选择2015年1月至2017年3月浙江省安吉县人民医院重症医学科(ICU)收治的82例MV危重患者,按随机数字表法分成容许性低热量喂养组(40例,非蛋白热量 $52.3\sim62.8\text{ kJ}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$,蛋白质 $1.2\sim1.5\text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$)和足量喂养组(42例,非蛋白热量 $104.6\sim125.5\text{ kJ}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$,蛋白质 $1.2\sim1.5\text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$),两组患者均于入ICU 24~48 h内按预期热量采用营养泵持续泵入瑞先进行肠内营养(EN),容许性低热量喂养组按预期热量的50%摄入,足量喂养组按预期热量100%摄入。分别于治疗前及治疗7 d检测患者营养指标[血清前白蛋白(PA)、白蛋白(ALB)]和炎症指标[血清降钙素原(PCT)、超敏C-反应蛋白(hs-CRP)],记录MV时间、ICU住院时间、每日胰岛素用量、28 d病死率,医院获得性肺炎(HAP)、泌尿系感染、感染性休克等继发感染发生情况,营养相关并发症发生情况。**结果** 与治疗前比较,两组患者治疗后血清PA、ALB均明显升高,PCT、hs-CRP明显下降[低热量喂养组:PA(mg/L)为 127.42 ± 65.83 比 80.92 ± 60.14 ,ALB(g/L)为 30.16 ± 4.32 比 25.36 ± 6.21 ,PCT(ng/L)为 375.8 ± 227.2 比 762.3 ± 314.5 ,hs-CRP(mg/L)为 32.19 ± 7.53 比 120.48 ± 60.24 ;足量喂养组:PA(mg/L)为 132.56 ± 61.32 比 86.78 ± 47.06 ,ALB(g/L)为 31.25 ± 4.63 比 26.71 ± 5.48 ,PCT(ng/L)为 412.1 ± 323.4 比 821.7 ± 408.6 ,hs-CRP(mg/L)为 35.86 ± 5.69 比 116.38 ± 72.16 ,均 $P<0.05$],但两组治疗后各指标差异并无统计学意义(均 $P>0.05$)。与足量喂养组比较,低热量喂养组治疗后MV时间(h: 162.35 ± 20.37 比 153.48 ± 18.65)、ICU住院时间(d: 7.52 ± 1.61 比 6.34 ± 1.87)、28 d病死率(17.5%比19.0%)、院内感染发生率(45.0%比47.6%)比较差异均无统计学意义(均 $P>0.05$),但每日胰岛素用量(U: 13.68 ± 10.36 比 26.24 ± 18.53)及呕吐、反流、腹胀、腹泻、便秘等营养相关并发症发生率(32.5%比54.8%)明显低于足量喂养组(均 $P<0.05$)。Kaplan-Meier生存曲线分析显示,两组28 d累积生存率差异无统计学意义($\chi^2=3.216$, $P=0.068$)。**结论** MV重症患者接受容许性低热量喂养的疗效及预后与足量喂养相当,但可减少胰岛素用量,且患者胃肠道耐受性更好。

【关键词】 容许性低热量喂养； 足量喂养； 机械通气； 预后

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Impact of permissive underfeeding versus standard enteral feeding on outcomes in critical patients requiring mechanical ventilation: a prospective randomized controlled study Ma Nianbin, Shen Mingfu, Wan Zhen, Pan Sijun, Liu Xian, Yao Zhongxiang

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【Abstract】Objective To compare the impact of permissive underfeeding versus standard enteral feeding on outcomes in critical patients requiring mechanical ventilation (MV). **Methods** A prospective randomized controlled study was conducted. Eighty-two patients requiring MV admitted to intensive care unit (ICU) of Anji People's Hospital from January 2015 to March 2017 were enrolled, and they were randomly divided into the permissive underfeeding group ($n=40$, non-protein heat was $52.3\sim62.8\text{ kJ}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, protein was $1.2\sim1.5\text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) and standard enteral feeding group ($n=42$, non-protein heat was $104.6\sim125.5\text{ kJ}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, protein was $1.2\sim1.5\text{ g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$). Permissive underfeeding group received 50% of their daily energy expenditure via enteral nutrition (EN) and standard enteral feeding group received 100% of their daily energy expenditure via EN in 24~48 hours after admitted to ICU. Nutritional status [pro-albumin (PA), serum albumin (ALB)], inflammation state [procalcitonin (PCT), hypersensitive C-reactive protein (hs-CRP)] were detected before treatment and 7 days after treatment. Duration of MV, length of ICU stay, daily insulin dosage, 28-day mortality, hospital acquired pneumonia (HAP), urinary tract infection, septic shock and other secondary infection, and the nutrition related complications were recorded. **Results** Compared with before treatment, the levels of serum PA (mg/L) and ALB (g/L) were significantly increased, the levels of PCT (ng/L) and hs-CRP (mg/L) were significantly decreased at 7 days after treatment in both groups [permissive underfeeding group: PA was 127.42 ± 65.83 vs. 80.92 ± 60.14 , ALB was 30.16 ± 4.32 vs. 25.36 ± 6.21 , PCT was 375.8 ± 227.2 vs. 762.3 ± 314.5 , hs-CRP was 32.19 ± 7.53 vs. 120.48 ± 60.24 ; standard enteral feeding group: PA was 132.56 ± 61.32 vs. 86.78 ± 47.06 , ALB was 31.25 ± 4.63 vs. 26.71 ± 5.48 , PCT was 412.1 ± 323.4 vs. 821.7 ± 408.6 , hs-CRP was 35.86 ± 5.69 vs. 116.38 ± 72.16 ,均 $P<0.05$], but there was no significant difference between the two groups in all indicators (all $P>0.05$). Compared with standard enteral feeding group, permissive underfeeding group had less daily insulin dosage (U: 13.68 ± 10.36 vs. 26.24 ± 18.53) and fewer complications related to nutrition (32.5% vs. 54.8%, $P<0.05$). Kaplan-Meier survival curve analysis showed that the cumulative survival rate of the two groups at 28 days was not significantly different ($\chi^2=3.216$, $P=0.068$). **Conclusion** MV critically ill patients receiving permissive underfeeding have similar efficacy and prognosis to those receiving standard enteral feeding, but can reduce insulin consumption, and patients have better tolerance of the gut.

vs. 86.78 ± 47.06 , ALB was 31.25 ± 4.63 vs. 26.71 ± 5.48 , PCT was 412.1 ± 323.4 vs. 821.7 ± 408.6 , hs-CRP was 35.86 ± 5.69 vs. 116.38 ± 72.16 , all $P < 0.05$], but there was no significant difference in PA, ALB, PCT or hs-CRP at 7 days after treatment between two groups (all $P > 0.05$). There was no significant difference in the duration of MV, length of ICU stay, 28-day mortality or ICU-associated infection between two groups [duration of MV (hours): 162.35 ± 20.37 vs. 153.48 ± 18.65 , length of ICU stay (days): 7.52 ± 1.61 vs. 6.34 ± 1.87 , 28-day mortality: 17.5% vs. 19.0%, ICU-associated infection: 45.0% vs. 47.6%, all $P > 0.05$]. Compared with standard enteral feeding, insulin demand was significantly decreased (U/d: 13.68 ± 10.36 vs. 26.24 ± 18.53), and gastrointestinal intolerance was less frequent (32.5% vs. 54.8%) in the permissive underfeeding group (both $P < 0.05$). Kaplan-Meier survival curve analysis showed that there was no significant difference between the two groups ($\chi^2 = 3.216$, $P = 0.068$). **Conclusion** The curative effect and prognosis of MV severe patients receiving permissive underfeeding are similar to those of standard enteral feeding, but it can reduce the dosage of insulin with better gastrointestinal tolerance.

【Key words】 Permissive underfeeding; Standard enteral feeding; Mechanical ventilation; Outcome

Fund program: Science and Technology Planning Project of Anji County in Zhejiang Province (201420)

重症医学科(ICU)中机械通气(MV)的危重症患者所占比例较大,这些患者常伴有急性呼吸功能不全、严重应激反应、分解代谢大于合成代谢、易出现各种程度的营养不良等情况^[1-3]。合理的营养对提高患者免疫力、减轻炎症反应^[4]、改善呼吸功能及临床预后具有重要意义。但如何为这些危重患者选择合适的营养摄入量却一直存在较大争议^[5]。有学者认为低热量喂养会引起不良临床结局^[6],而另一些学者则认为接受低热量喂养的危重症患者耐受性更好,预后更佳^[7]。本研究旨在对照观察容许性低热量喂养与足量喂养对危重症MV患者新陈代谢和预后的影响。

1 资料与方法

1.1 病例的纳入和排除标准:采用前瞻性随机对照研究方法,选择2015年1月至2017年3月本院ICU收治的需要MV辅助呼吸的危重症患者82例。

1.1.1 入选标准:入院需MV≥3 d;预计需人工喂养>3 d;年龄20~80周岁。

1.1.2 排除标准:血流动力学不稳定;严重水、电解质紊乱和酸碱失衡;孕产妇;消化道出血、肠梗阻、急性胰腺炎及恶性肿瘤终末期患者。

1.1.3 剔除标准:疗程中病情迅速恶化、发生多器官功能衰竭(MOF)。

1.2 伦理学:本研究符合医学伦理学标准,经医院伦理委员会批准(审批号:2014-10),均获得患者家属知情同意。

1.3 分组:采用随机数字表法将患者分为容许性低热量喂养组(40例)和足量喂养组(42例)。

1.4 治疗方法:入ICU后建立人工气道行MV;常规抗炎、抑酸护胃预防应激性溃疡、止咳、祛痰、平喘等治疗;如治疗过程中出现呕吐、反流、腹胀、腹泻或便秘等症状立即对症治疗;微泵持续静脉泵入普通胰岛素控制血糖在4.4~10.0 mmol/L。入ICU

12~24 h 内置入胃管或空肠营养管,回抽后无明显胃潴留即给予温开水200 mL,观察30 min后开始采用营养泵持续泵入瑞先(费森尤斯卡比华瑞制药有限公司)进行肠内营养(EN)治疗,热量4184 kJ/L,起始滴速25 mL/h,逐渐加快至目标摄入量。当肠内输入量增加时,每6 h 测定1次胃残余量(GRV)。EN不足部分用肠外营养(PN)补充。1周后仍未脱机的MV患者统一采用足量喂养EN支持。

1.4.1 容许性低热量喂养组:每日给予预期热量的50%,其中非蛋白热量52.3~62.8 kJ·kg⁻¹·d⁻¹,蛋白质1.2~1.5 g·kg⁻¹·d⁻¹。

1.4.2 足量喂养组:计算目标摄入量,按预期热量100%摄入,非蛋白热量104.6~125.5 kJ·kg⁻¹·d⁻¹,蛋白质1.2~1.5 g·kg⁻¹·d⁻¹。

1.5 收集资料:①基线指标:记录患者的性别、年龄;入院时的急性生理学与慢性健康状况评分系统Ⅱ(APACHEⅡ)评分;主要入院诊断。②营养指标:于营养治疗前及治疗7 d,使用瑞士罗氏公司Cobas c702全自动生化分析仪,采用免疫比浊法和溴甲酚绿比色法分别测定血清前白蛋白(PA)、白蛋白(ALB)水平。③炎症指标:使用罗氏Cobas e-602全自动免疫分析仪,采用电化学发光法测定血清降钙素原(PCT)水平;使用芬兰Orion Diagnostica公司QuikRead go POCT检测系统,采用免疫比浊法测定血清超敏C-反应蛋白(hs-CRP)水平。④预后指标: MV时间、ICU住院时间、每日胰岛素用量、28 d病死率;医院获得性肺炎(HAP)、泌尿系感染、感染性休克等继发感染发生情况;腹泻、腹胀、呕吐、反流等营养并发症发生情况。

1.6 统计学分析:使用SPSS 17.0软件分析数据。计数资料用率表示,组间比较采用 χ^2 检验;正态分布计量资料以均数±标准差($\bar{x} \pm s$)表示,组间比较采用独立样本t检验;28 d生存曲线分析采用

Kaplan-Meier 法。 $P < 0.05$ 为差异有统计学意义。

2 结 果

2.1 两组患者一般资料比较(表1):两组患者性别、年龄、APACHE II 评分、主要入院诊断等基线资料比较差异均无统计学意义(均 $P > 0.05$),说明两组基线资料均衡,具有可比性。

2.2 两组患者营养、炎症指标变化比较(表2):两组治疗前营养、炎症等指标比较差异均无统计学意义。与治疗前比较,两组治疗 7 d 血清 ALB、PA 均明显升高, PCT、hs-CRP 均明显下降(均 $P < 0.05$),但两组间比较差异均无统计学意义(均 $P > 0.05$)。

2.3 两组患者预后指标比较(表3):低热量喂养组患者每日胰岛素用量明显低于足量喂养组($P < 0.05$)。低热量喂养组有 7 例、足量喂养组有 8 例患者死于 MOF,两组患者 28 d 病死率差异无统计学意义($P > 0.05$)。两组患者 MV 时间、ICU 住院时间、院内感染发生率比较差异均无统计学意义(均 $P > 0.05$)。

表 3 不同喂养方式两组 MV 重症患者预后指标比较

组别	例数 (例)	每日胰岛素用量 (U, $\bar{x} \pm s$)	MV 时间 (h, $\bar{x} \pm s$)
低热量喂养组	40	13.68 ± 10.36	162.35 ± 20.37
足量喂养组	42	26.24 ± 18.53	153.48 ± 18.65
<i>t</i> 值		2.149	0.835
<i>P</i> 值		0.030	0.500
组别	例数 (例)	ICU 住院时间 (d, $\bar{x} \pm s$)	院感发生率 [% (例)]
低热量喂养组	40	7.52 ± 1.61	45.0 (18)
足量喂养组	42	6.34 ± 1.87	47.6 (20)
<i>t</i> / χ^2 值		1.380	5.240
<i>P</i> 值		0.450	0.126
注: MV 为机械通气, ICU 为重症医学科			

2.4 两组患者胃肠道耐受情况比较:两组有部分患者出现轻微的胃肠道不良反应,包括呕吐、反流、腹胀、腹泻、便秘等,低热量喂养组发生率明显低于足量喂养组[32.5% (13/40) 比 54.8% (23/42), $\chi^2 = 4.120, P < 0.05$],两组未发现其他严重不良反应。

2.5 两组患者 28 d 生存曲线分析(图1):两组患者 28 d 累积生存率差异无统计学意义($\chi^2 = 3.216, P = 0.068$)。

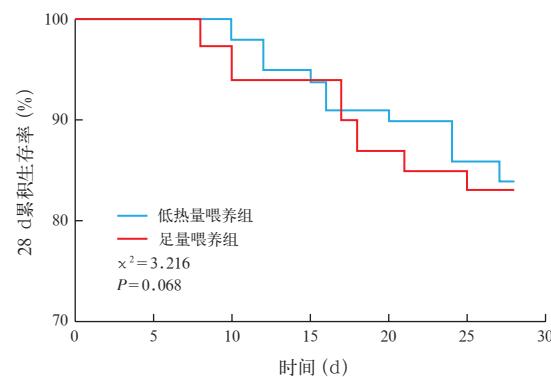


图 1 不同喂养方式两组机械通气(MV)重症患者 28 d Kaplan-Meier 生存曲线

3 讨 论

营养支持作为改善重症患者预后必不可少的措施已被广泛接受,目前危重患者使用 EN 已成为共识,但如何选择理想的喂养量还未明确。众所周知,重症患者因应激反应导致机体长期处于高分解代谢状态,持续喂养不足必然导致营养不良的发生,引起伤口感染、愈合延迟,MOF 等发生率上升,MV 和住院时间延长^[1, 6, 8]。对于具有营养不良高风险或严重营养不良的重症患者,足量喂养仍是首选^[9]。然而很多情况下足量喂养也存在弊端,受限于患者胃

表 1 不同喂养方式两组 MV 重症患者一般资料比较

组别	例数 (例)	性别(例)		年龄 (岁, $\bar{x} \pm s$)	APACHE II (分, $\bar{x} \pm s$)	主要入院诊断[例(%)]				
		男性	女性			急性心衰	脑血管意外	多发伤	COPD	其他
低热量喂养组	40	31	9	62.7 ± 11.4	20.6 ± 8.2	8 (20.0)	7 (17.5)	10 (25.0)	8 (20.0)	7 (17.5)
足量喂养组	42	30	12	65.3 ± 12.5	22.8 ± 7.4	10 (23.8)	9 (21.4)	9 (21.4)	7 (16.7)	7 (16.7)
χ^2/t 值		0.400	0.432	0.515		0.173	0.205	0.157	0.152	0.019
<i>P</i> 值		0.782	0.412	0.124		0.112	0.725	0.536	0.427	0.922

注: MV 为机械通气, APACHE II 为急性生理学与慢性健康状况评分系统 II, COPD 为慢性阻塞性肺疾病

表 2 不同喂养方式两组 MV 重症患者营养、炎症指标变化比较($\bar{x} \pm s$)

组别	例数 (例)	PA (mg/L)		ALB (g/L)		PCT (ng/L)		hs-CRP (mg/L)	
		治疗前	治疗 7 d	治疗前	治疗 7 d	治疗前	治疗 7 d	治疗前	治疗 7 d
低热量喂养组	40	80.92 ± 60.14	127.42 ± 65.83 ^a	25.36 ± 6.21	30.16 ± 4.32 ^a	762.3 ± 314.5	375.8 ± 227.2 ^a	120.48 ± 60.24	32.19 ± 7.53 ^a
足量喂养组	42	86.78 ± 47.06	132.56 ± 61.32 ^a	26.71 ± 5.48	31.25 ± 4.63 ^a	821.7 ± 408.6	412.1 ± 323.4 ^a	116.38 ± 72.16	35.86 ± 5.69 ^a
<i>t</i> 值		0.188	0.149	0.418	0.479	0.349	0.300	0.128	0.944
<i>P</i> 值		0.214	0.198	0.326	0.257	0.108	0.110	0.436	0.178

注: MV 为机械通气, PA 为前白蛋白, ALB 为白蛋白, PCT 为降钙素原, hs-CRP 为超敏 C-反应蛋白;与本组治疗前比较,^a $P < 0.05$

肠耐受等情况,临床难以有效实施。ICU中MV患者较为普遍,常因镇静肌松制动等因素导致EN中断停止而无法达到足量喂养^[1, 10],于是有学者提出了容许性低热量喂养的概念^[11]。一项单中心随机对照试验(RCT)证明,容许性低热量喂养比足量喂养更能改善重症患者的预后^[12]。2012年“拯救脓毒症运动”倡议也建议脓毒症早期应用容许性低热量营养支持^[13]。鉴于理想喂养策略存在争议,且ICU中MV患者的营养治疗非常普遍,本研究旨在进一步验证容许性低热量喂养与足量喂养对MV重症患者预后的影响。

ICU中MV患者大多处于镇静镇痛制动状态,其实际能量消耗可能与静息能量消耗一致,所以以静息能量作为能量目标值可能更接近患者的能量需求^[14-15]。2016年美国肠外肠内营养学会(ASPEN)重症患者营养支持指南指出:在没有间接能量测定法(如能量代谢车)的情况下,重症患者能量供给目标为 $104.6 \sim 125.5 \text{ kJ} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ^[9],本研究据此制定患者的目标摄入量。

国内多项研究显示,PCT、hs-CRP与炎症反应相关,可以作为监测细菌感染、判断病情预后及疗效的可靠指标^[16-17]。本研究显示,两组患者治疗后血清PA、ALB均显著高于治疗前,PCT、hs-CRP均显著低于治疗前。说明容许性低热量喂养和足量喂养均可以改善MV重症患者的代谢状态,减轻炎症反应,且二者作用一致,这与许多大样本研究结果相似^[18-19]。

曾经推崇EN早期容许性低热量治疗的Arabi等^[18]在一项多中心大样本RCT研究中发现,足量喂养组与容许性低热量喂养组重症患者院内感染发生率、MV时间、ICU住院时间、总住院时间和28、90、180 d病死率差异均无统计学意义,区别在于低热量喂养组患者血糖控制得更好,胰岛素用量较少,需要持续血液净化的比例较低,与本研究结果类似。有学者发现,低热量喂养与患者院内感染发生率存在相关性^[20],考虑系患者病种偏差导致,因该研究中低热量喂养组患者患糖尿病、慢性阻塞性肺疾病(COPD)的比例高于正常热量喂养组,这些合并慢性基础疾病的患者可能更容易发生院内感染。一项针对脓毒症患者的研究显示,与正常热量营养比较,低热量、高热量营养支持后患者28 d病死率差异无统计学意义,但60 d病死率可明显增高^[21]。这可能因为:各研究入组患者异质性、观察周期、营养治疗方

案均不同,补充蛋白质目标量无统一标准。本研究营养方案为非蛋白热量,两组患者均同时按目标量补充蛋白,将蛋白质不足因素对预后的影响降至最小。有研究显示,最佳蛋白质和营养量的结合可以降低MV危重患者的病死率^[22]。Arabi等^[12]的一项单中心RCT研究显示,与足量喂养组比较,容许性低热量喂养组患者28 d病死率无明显差异,而180 d病死率却明显下降。这可能与足量喂养组可能并没有完全达到目标摄入量,容许性低热量喂养的量还不够低,以致对重症患者短期预后影响并不显著,而长期预后却有明显改善有关。但随后Arabi等^[18]的多中心大样本RCT研究却表明,容许性低热量治疗患者长期预后也未改善。尽管这两项研究中关于低热量界定范围有所不同,我们仍不得不重新审视EN早期实施容许性低热量喂养治疗的必要性。

本研究还显示,足量喂养组恶心呕吐、腹泻腹胀等胃肠道反应发生率明显高于低热量喂养组,这一结果也得到国外多项类似研究论证支持。有学者认为50%的MV患者会出现不同程度的胃肠道并发症,如肠鸣音减弱、胃排空延迟及腹泻等^[23];Thibault等^[24]研究发现,给予大于目标量60%的EN同时抗感染治疗可增加患者的腹泻发生率;Petros等^[25]认为,低热量喂养重症患者胃肠道不耐受发生率较正常热量喂养者下降。

本研究中受患者胃肠耐受性影响,为了弥补目标摄入量的不足部分,少量使用了PN。但在ICU中使用PN目前也存在争议。有学者发现早期添加PN引起院内感染的发生率上升,ICU住院时间延长,但对病死率没有影响^[26]。但学术界也有不同的意见,王国锋等^[27]发现,EN+PN复合营养有利于脑损伤患者更早恢复。

本研究也存在很多不足:①为单中心研究,且样本量较少,随机误差较大,入组患者存在异质性。②喂养方式因患者胃肠耐受反应的影响而采用EN+PN的联合方式,可能对患者营养指标存在一定的影响。③受研究设计限制,本研究观察患者的短期预后,而非长期预后,延长观察时间可能会发现不同的结果。

综上,本研究显示,容许性低热量喂养和足量喂养对改善MV重症患者的28 d预后效果一致,但低热量喂养可减少每日胰岛素用量,且胃肠道耐受性更好,该研究结果有待更多更大规模、设计更加完善的高质量RCT研究进一步评估。

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