doi: 10.13241/j.cnki.pmb.2020.15.026

诺欣妥联合心脏运动康复对射血分数降低的心力衰竭疗效的研究 *

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摘要 目的：探讨诺欣妥联合心脏运动康复对射血分数降低（HFrEF）的心力衰竭（HF）的临床疗效。**方法：**将我院心内科于 2018 年 1 月 ~2019 年 4 月收治的 70 例 HFrEF 患者随机分为两组，各 35 例。对照组均给予诺欣妥规范治疗，实验组在此基础上根据心肺运动测试（CPET）测得代谢当量制定个性化心脏运动康复，包括院内、院外心脏康复干预及定期随访，为期 6 个月。采用彩色心脏超声诊断仪、心肺运动测试（CPET）分析两组治疗前后心肺功能变化，同时观察住院及随访期间的预后情况。**结果：**治疗 6 个月后，两组左心室舒张末期内径(LVEDD)、左室收缩末期内径（LVESD）、左心室射血分数(LVEF) 均明显改善，且实验组显著优于对照组 (P<0.05)。治疗 6 个月后，实验组 AT 明显升高，峰值 VO_2/kg、峰值 VO_2 水平均有一定程度上升，且明显优于对照组 (P<0.05)。与对照组比较，实验组 90d 内 HF 再住院率（8.6%vs.28.6%）、随访期间 MACEs 发生率（17.1%vs.40.0%）均显著降低（P<0.05）。**结论：**诺欣妥联合心脏运动康复治疗可使 HFrEF 患者显著获益，在改善心肺功能、运动能力及近期预后方面疗效显著，可作为 HFrEF 患者的一线治疗方案。

关键词：心力衰竭；射血分数降低；诺欣妥；心脏运动康复

中图分类号：R541.61 **文献标识码：**A **文章编号：**1673-6273(2020)15-2930-04

Effect of Entresto Combined with Cardiac Exercise Rehabilitation in Heart Failure Patients with Reduced Ejection Fraction*

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ABSTRACT Objective: To explore the effect of entresto combined with cardiac exercise rehabilitation in heart failure patients with reduced ejection fraction (HFrEF). **Methods:** 70 patients with HFrEF admitted to the department of cardiology of our hospital From January 2018 to April 2019 were randomly divided into two group. The control group (n=35) was given standard treatment with entresto, and the experimental group (n=35) was formulated personalized cardiac exercise rehabilitation based on the metabolic equivalent measured by cardiopulmonary exercise test (CPET), including in-hospital and out-of-hospital cardiac rehabilitation intervention and regular follow-up for 6 months. Color echocardiography and cardiopulmonary exercise (CPET) were used to analyze the changes of cardiopulmonary function before and after treatment in the two groups, and the prognosis during hospitalization and follow-up was observed. **Results:** After 6 months of treatment, the levels of left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), left ventricular ejection fraction, (LVEF) were significantly improved in both groups, and the indicators in the experimental group was significantly better than those in the control group (P<0.05). After 6 months of treatment, the AT of the experimental group was significantly increased, levels of peak VO_2/kg and peak VO_2 were also significantly increased, and were significantly better than those in the control group (P<0.05). Compared with the control group, the HF rehospitalization rate within 90d (8.6%vs.28.6%) and MACEs incidence (17.1% vs.40.0%) in the experimental group were significantly reduced (P<0.05). **Conclusions:** Entresto combined with cardiac exercise rehabilitation therapy can be significantly beneficial for HFrEF patients, it has significant efficacy in improving cardiopulmonary function, motor ability and short-term prognosis, which can be used as the first-line treatment for HFrEF patients.

Key words: Heart failure; Reduced ejection fraction; Entresto; Cardiac exercise rehabilitation

Chinese Library Classification(CLC): R541.61 Document code: A

Article ID: 1673-6273(2020)15-2930-04

前言

心力衰竭（HF）是多数心脏疾病的终末阶段，预后差、致死性高，严重威胁患者生存质量和生命健康。临床上将左心室射血分数（LVEF）<40%的 HF 称为射血分数降低的心力衰竭（HFrEF），约占所有 HF 的 40%~70%，其 5 年死亡率不足

* 基金项目：国家自然科学基金项目（8177020586）；上海市浦东新区临床高原学科项目（PWYgy2018-05）

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（收稿日期：2019-12-31 接受日期：2020-01-27）

50%[1]。沙库巴曲缬沙坦(商品名:诺欣妥)是一种新型血管紧张素受体 - 脑啡肽酶双重阻断剂(ARNI),通过拮抗血管紧张素受体、抑制血管紧张素酶 II 和脑啡肽酶发挥对心力衰竭的治疗作用,美国心脏病学会和心脏学会(ACC/AHA)于 2017 年将其作为 II~III 级 HFrEF 患者的 I 类推荐药物,但该药仍处于早期临床应用阶段[2,3]。近年来,国内外对于 HF 患者的心脏康复愈发重视,研究表明早期心脏康复在改善运动耐量、生存质量及近期预后具有明显疗效[4-6]。为了进一步提高 HFrEF 的临床疗效,本研究尝试对 HFrEF 患者采用诺欣妥辅以心脏康复治疗,探讨该方案对患者心功能及预后的影响。

1 资料与方法

1.1 研究对象

收集我院心内科于 2018 年 1 月 ~2019 年 4 月收治的 70 例 HFrEF 患者。纳入标准:① 均符合中华医学会心血管病学分会发布的《中国心力衰竭诊断和治疗指南 2014》[7]的诊断标准,LEVF<40%;② 年龄≤ 70 岁,纽约心功能分级(NYHA)II~IV 级;③ 排除严重先天性心脏病、瓣膜疾病、心肌病、未控制的严重感染、诺欣妥禁忌或过敏、无法耐受心肺运动测试(CPET)、严重肝肾功能不全者。其中男性 39 例,女性 31 例;年龄 42~70(57.6±4.8)岁;体质量指数(BMI)20.1~25.6(23.0±1.7)kg/m^2;心衰病程 2.7~10.9(5.5±1.6)年;NYHA 分级:II 级 21 例,III 级 35 例,IV 级 14 例。采用随机数字表法,将所有患者分为实验组与对照组,各 35 例。本研究符合《世界医学协会赫尔辛基宣言》相关要求,患者或其近亲属均知情同意。

1.2 方法

1.2.1 一般治疗 所有 HFrEF 患者入院后均给予 HF 标准化治疗,包括 ACEI/ 血管紧张素受体阻滞剂(ARB)、醛固酮受体拮抗剂及β 受体阻滞剂等 " 金三角 " 药物,同时口服诺欣妥(北京诺华制药有限公司,批准文号:H20170344,50 mg/ 片),起始剂量 50 mg/ 次,每天 2 次,根据患者病情及耐受程度每隔 2-4 周增加 1 倍,逐步调整至 200 mg/ 次并作为维持剂量,每天 2 次。所有患者均连续治疗 10 周。

1.2.2 研究组 给予个性化的早期心脏康复方案[8],具体分为以下几个方面:

院内康复期:患者进入心衰稳定期后,根据心肺运动测试(CPET)测定的代谢当量,并制定个性化的康复训练方案。① 运动形式:跑步机训练或踏车训练等;② 运动时间:初始为 60 min,根据运动能力,可分为一次 60 min 或一次 30 min,1 天 2 次;③ 运动频率:每周 5 次;④ 运动强度由无氧阈(AT)时测得的代谢当量(METS)或下肢阻力强度经计算酌情制定。由专业医护人员根据靶心率结果调整运动强度,运动中出现乏力、疲劳等不适症状时应降低运动强度或停止运动。

院外康复期:以有氧运动为主,包括 5 min 的预热拉伸,30 min 的有氧运动,具体项目有步行、慢跑、踏车、太极等,以及 5 min 的冷却拉伸。以自觉劳累为度,可根据身体状况及靶心率逐渐增加运动时间与强度。

定期随访:出院时,给予每位患者《心力衰竭心脏康复手册》,交待心脏运动康复的相关注意事项,包括风险因素控制,饮食、运动和用药指导,持续心脏康复训练等。出院后定期电话随访和监督,首月为 1 次 / 周,之后调整为 1 次 / 月,鼓励患者积极与医务人员沟通。

1.3 观察指标

1.3.1 心功能评估 采用 Aloka SSD-4000 型彩色心脏超声诊断仪评估患者的心功能,具体指标包括左心室舒张末期内径(LVEDD)、左室收缩末期内径(LVESD),并根据公式计算左心室射血分数(LVEF)。治疗前、治疗 6 个月后各评估一次。

1.3.2 CPET 采用意大利 cosmed 心肺运动评估系统,采用踏车负荷试验监测安静时、运动期及恢复期心率、血压、12 导联型心电图、氧代动力学等指标。利用软件自带系统导出所有相关指标,包括无氧阈值(AT)、最大公斤摄氧量(peak VO_2/Kg)、峰值耗氧量(VO_2 peak)。治疗前、治疗 6 个月后各测试一次。

1.3.3 近期预后 观察两组患者住院期间全因死亡和 HF 再住院情况,出院后跟踪随访 6 个月,记录期间患者出现的室性心律失常、HF 再住院、心源性死亡等不良心脏事件(MACEs)。

1.4 统计学方法

采用 SPSS 18.0 版统计软件包。计量资料以均数±标准差($\bar{x}\pm s$)表示,比较采用独立样本或配对样本 t 检验;计数资料以例数(%)表示,比较采用 x^2 检验。

2 结果

2.1 两组一般资料比较

两组患者在年龄、性别、NYHA 分级、心衰病程等方面,差异均无统计学意义(P>0.05)。见表 1。

2.2 两组治疗前后心功能指标变化比较

治疗前,两组 LVEDD、LVESD、LVEF 主要心功能指标比较,差异均无统计学意义(P>0.05);治疗 6 个月后,上述指标在两组患者中均明显改善,且实验组显著优于对照组,差异均有

表 1 两组一般资料比较

Table 1 Comparison of general data between the two groups

Groups	N	Gender (male/female)	Age (year)	BMI (kg/m^2)	Disease course of heart failure (year)	NYHA grading		
						II	III	IV
Experimental group	35	19/16	57.1±4.4	23.6±1.4	5.6±1.7	13	16	6
Control group	35	20/15	58.2±5.0	22.8±2.0	5.3±1.4	8	19	8
t/χ^2		0.06	0.98	1.94	0.81		1.733	
P		0.810	0.332	0.057	0.423		0.420	

统计学意义(P<0.05)。见表 2。

表 2 两组治疗前后心功能指标比较($\bar{x}\pm s$)

Table 2 Comparison of cardiac function indexes before and after treatment between the two groups($\bar{x}\pm s$)

Groups	N		LVESD(mm)	LVEDD(mm)	LVEF(%)
Experimental group	35	Before treatment	42.51±3.53	70.11±6.62	38.54±4.24
		6 months after treatment	35.74±1.46[◎△]	54.76±4.54[◎△]	52.47±5.43[◎△]
Control group	35	Before treatment	43.15±3.80	71.35±6.05	39.17±4.62
		6 months after treatment	37.26±2.37[◎]	60.29±5.38[◎]	45.26±5.83[◎]

Note: Compared with before treatment, [◎] P<0.05; Treatment for 6 months between groups, [△] P<0.05.

2.3 两组治疗前后 CEPT 指标比较

治疗前,两组 CEPT 相关指标比较,差异均无统计学意义(P>0.05);治疗 6 个月后,实验组 AT、峰值 VO_2/kg、峰值 VO_2 水平明显升高,且明显优于对照组,差异均有统计学意义(P<0.05)。见表 3。

表 3 两组治疗前后 CEPT 指标比较($\bar{x}\pm s$)

Table 3 Comparison of CEPT indexes before and after treatment between the two groups($\bar{x}\pm s$)

Groups	N		AT ($mL\cdot kg^{-1}\cdot min^{-1}$)	peak VO_2/kg ($mL\cdot kg^{-1}\cdot min^{-1}$)	peak VO_2 (mL/min)
Experimental group	35	Before treatment	9.59±1.57	14.81±3.46	1285.06±106.81
		6 months after treatment	15.26±7.63[◎△]	19.25±2.88[◎△]	1486.13±125.09[◎△]
Control group	35	Before treatment	9.47±1.48	14.92±3.51	1270.19±121.28
		6 months after treatment	12.79±2.16[◎]	17.23±3.57[◎]	1374.78±105.19[◎]

Note: Compared with before treatment, [◎] P<0.05; Treatment for 6 months between groups, [△] P<0.05.

2.4 两组近期预后比较

两组住院期间全因死亡(心源性猝死、多脏器功能衰竭、心衰加重死亡)率比较,差异无统计学意义(P>0.05);与对照组比较,实验组 90d 内 HF 再住院率、随访期间 MACEs 发生率均显著降低,差异均有统计学意义(P<0.05)。见表 4。

表 4 两组近期预后比较[n(%)]

Table 4 Comparison of short-term prognosis between the two groups [n(%)]

Groups	N	All deaths occurred during hospitalization			HF rehospitalization rate within 90 days	MACEs during follow-up
		Sudden cardiac death	Multiple organ failure	Death because of aggravating heart failure		
Experimental group	35	1(2.9)	0(0)	1(2.9)	3(8.6)	6(17.1)
Control group	35	2(5.7)	2(5.7)	3(8.6)	10(28.6)	14(40.0)
χ^2			3.19		4.63	4.48
P			0.074		0.031	0.034

3 讨论

近年来 HFrEF 的治疗愈发引起重视,治疗目标不再局限于改善症状、提高生活质量,已由以往的强心、利尿、抗凝剂扩血管等转变为肾素 - 血管紧张素 - 醛固酮系统(RAAS)及神经内分泌调控治疗策略,进而逆转或延缓心室重构[9,10]。诺欣妥具有阻断 RAAS 的 AngⅡ受体和抑制脑啡肽酶的双重作用靶点,是 HF 治疗领域的突破性进展,被视为治疗 HF 的基石性药物。临床研究证实,诺欣妥可显著改善心肌损伤、心衰严重程度,并降低病死率,且与 ACEI/ARB 等其他抗治疗 HF 的药物联合使用具有较好的安全性和耐受性[11,12]。陈莉等[13]研究表明,欣诺妥可明显改善 HFrEF 的心衰患者的 N 末端 B 型利钠肽原(NT-proBNP)、超敏 C 反应蛋白(hs-CRP)、可溶性 ST2(sST2)等反映心功能的敏感指标,改善生活质量和预后。

心脏康复属于一种无氧阈值内的运动,可预防心肌缺血及心肌梗死等心血管突发事件,常用于 PCI 术后的康复管理[14-16]。Mahnaz 等[17]研究证实,心脏康复运动具有调节 RAAS 和交感神经活性的功能,可促进血管内皮细胞修复,提高心脏的代谢水平。Saito 等[18]研究发现,心肌康复运动有助于抑制炎性因子过表达,增加心肌、骨骼肌的有氧代谢,减少心肌血管阻力,并

可降低冠心病患者出现心绞痛的阈值。我国心脏康复起步较晚，至今尚仍缺乏统一的标准程序，多采用快速康复模式，持续时间短，缺乏系统性[19,20]，且其与欣诺妥联合应用的研究仍鲜有报道。本研究根据心肺运动试验制定个性化的运动处方，包含康复教育、危险因素控制、生活方式指导等全方位的干预，优化心脏康复训练的路径和程序[21-23]。结果显示，两组治疗 6 个月后 LVEDD、LVESD、LVEF 均明显改善，且实验组显著优于对照组 (P<0.05)，说明诺欣妥联合心脏康复运动可促进 HFrEF 患者心脏泵功能的恢复与心功能的改善，Leprêtre 与等[24]研究结果一致。

CEPT 是评价心肺功能的一种重要方式，其中 AT、峰值 VO_2/kg、峰值 VO_2 均是评价机体心肺功能与运动能力情况的敏感指标，同时可反映 HF 患者的预后[25-27]。本研究发现，实验组治疗 6 个月后 AT、峰值 VO_2/kg、峰值 VO_2 水平均明显上升，且明显优于对照组 (P<0.05)，说明在诺欣妥药物治疗基础上，联合心脏康复运动可增强 HF 患者的心肺功能和氧利用率，提高代谢当量，提升运动能力。此外，在预后方面，两组分别有 5 例、7 例死于心源性猝死、多脏器功能衰竭、心衰加重，虽两组全因死亡率未见显著性差异(P>0.05)，但实验组 30d 内 HF 再住院率(8.6%vs.28.6%)、随访期间 MACEs 发生率(17.1%vs.40.0%)均较对照组显著降低(P<0.05)，说明诺欣妥联合心脏运动康复有助于改善患者的预后。Safiyari 等[28]研究显示，居家心脏康复实施 3 个月后，HF 患者全因死亡率下降 15%~45%，心血管死亡率下降 10%~35%。另外，心脏康复过程中，健康教育、服药指导、定期复查等均有助于加强患者对疾病危险因素的认知，提高随访率，进而预防终点事件的发生[29,30]。

综上所述，诺欣妥联合心脏运动康复治疗可使 HFrEF 患者显著获益，在改善心肺功能、提高运动能力及近期预后方面疗效显著，可作为 HFrEF 患者的一线治疗方案。考虑到本研究样本量较少，且随访观察不长，因此远期预后有待积累更多样本进一步论证。

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