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超大剂量 ARB 治疗不同年龄扩张型心肌病合并心力衰竭患者的临床疗效和安全性研究 *

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摘要 目的:探讨超大剂量 ARB 治疗不同年龄扩张型心肌病(dilated cardiomyopathy,DCM)合并心力衰竭患者的临床疗效和安全性。**方法:**选择 2012 年 9 月 -2015 年 6 月西京医院心内科收治的 117 例 DCM 合并心衰的住院患者并将其随机分为 60 岁及以上年龄超大剂量(32 例,老年超大剂量组)及常规剂量(34 例,老年常规剂量组)ARB 治疗组;30 岁及以下年龄超大剂量(24 例,青年超大剂量组)和常规剂量(27 例,青年常规剂量组)ARB 治疗组。超大剂量组长期接受 ARB(缬沙坦,320-720 mg bid)治疗,常规剂量组长期接受 ARB(缬沙坦 80-240 mg bid)治疗。进行临床随访,比较各组患者全因死亡率、心衰再入院率及左室射血分数(LVEF)值等。**结果:**超大剂量组与常规剂量组、老年超大剂量组与老年常规剂量组年龄、性别、BMI、心率、收缩压、舒张压、心功能、高血压人数及比例、LVEF 值等临床基线资料比较差异均无统计学意义(*P>0.05*);青年常规剂量舒张压显著高于青年超大剂量组(*P<0.05*),但两组其它基线资料均无统计学差异。经过平均 28.18± 9.38 月的治疗和随访,超大剂量组全因死亡率、心衰再住院率显著低于常规剂量组(*P<0.05*);老年超大剂量组全因死亡率、心衰再住院率显著低于老年常规剂量组(*P<0.05*);青年超大剂量组心衰再住院率显著低于青年常规剂量组(*P<0.05*),但全因死亡率无统计学差异。各组患者治疗后 LVEF 值均较治疗前有明显提高,且超大剂量组、老年超大剂量组、青年超大剂量组的 LVEF 值均显著高于其常规剂量组(*P<0.05*)。超大剂量组和常规剂量组都发生了低血压、肝功损害、肾功损害等不良反应,但两组各项不良反应发生率比较无统计学差异。**结论:**超大剂量 ARB 治疗 DCM 合并心衰患者比常规剂量治疗能更大程度上降低死亡率和心衰再住院率,改善心功能也更加明显;但超大剂量 ARB 治疗青年 DCM 合并心衰患者仅能进一步降低心衰再住院率,不能降低全因死亡率;在院内严密监护下,超大剂量 ARB 治疗扩心病合并心衰安全可行。

关键词:扩张型心肌病;心力衰竭;不同年龄段;超大剂量;ARB

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A Retrospective Study on Supramaximal-dose ARB in the treatment of Dilated Cardiomyopathy Patients Complicated with Heart Failure with Different Ages*

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ABSTRACT Objective: To discuss the clinical efficacy and safety of supramaximal dose of ARB in the treatment of different ages of patients with dilated cardiomyopathy (DCM) complicated with heart failure. **Methods:** 117 cases of DCM patients treated in Xi Jing hospital from September 2012 to June 2015 were selected and randomized into the supramaximal-dose group and the normal-dose group, each group were subdivided into ≥ 60 years old and ≤ 30 years old groups. Patients in the supramaximal-dose group were treated with valsartan (320-720 mg bid) while patients in the normal-dose group were given valsartan (80-240 mg bid). These patients were followed-up and the rate of all cause death and hospitalization due to heart failure as well as the LVEF were compared between different groups. **Results:** There was no significant difference between the supramaximal-dose group and the normal-dose group, or the old supramaximal-dose group and the old normal-dose group in the clinical baseline data such as age, gender, BMI, heart rate, systolic/diastolic pressure, cardiac function, percentage of hypertension, LVEF, and Pro-BNP levels. Although the average diastolic pressure of young normal-dose group was significantly higher than that of the young supramaximal-dose group (*P<0.05*), there was no significant difference between the two groups in other baseline data mentioned above. After a period of treatment as long as 28.18± 9.38 months on average, the all cause death rate and hospitalization rate of supramaximal-dose group and old supramaximal-dose group were

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significantly lower than those of the normal-dose group respectively ($p<0.05$). The young supramaximal-dose group failed to achieve significant difference in the all cause death rate compared with the young normal-dose group although its hospitalization risk was much lower ($P<0.05$). All the groups show an obvious improvement of LVEF after the treatment. The LVEF of supramaximal-dose, old supramaximal-dose, young supramaximal-dose group were significantly higher than their normal-dose groups($p<0.05$). When it comes to the safety, main adverse effects such as hypotension, impaired liver and renal function were found both in the supramaximal-dose group and the normal-dose group. However, there was no difference between the two groups in these items. **Conclusion:** Compared with normal-dose ARB, long-term supramaximal-dose ARB could significantly reduce the risk of all cause death and hospitalization as well as improve the cardiac function in the treatment of DCM patients with heart failure, which is the same as the result of supramaximal-dose of ARB treatment in the old DCM patients with heart failure. As for the young DCM patients with heart failure, supramaximal-dose of ARB treatment couldn't reduce the hospitalization rate but failed to show any benefit in reducing the risk of all cause death. Importantly, supramaximal-dose of ARB was safe and feasible under the in-hospital supervision and proper management in the treatment of DCM patients with heart failure.

Key words: Dilated cardiomyopathy; Heart failure; Different age groups; Supramaximal dose; ARB

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前言

扩张型心肌病(Dilated cardiomyopathy,DCM)是一种以左心室腔扩大伴收缩功能障碍为特征的全心扩张性疾病,是导致心脏移植最常见的原因,也是引起心力衰竭的第三大常见原因[1], 临床上 DCM 以治疗心衰为主。目前,RAAS 抑制剂(ACEI/ARB)、醛固酮受体拮抗剂以及拮抗交感神经激活的β 受体阻滞剂(即心衰治疗的 " 金三角 ")是临床上治疗心衰的重要手段。但对于许多 DCM 心衰患者而言,其疗效仍不容乐观且很多患者会发展至终末期心衰。

在心衰治疗中,ACEI/ARB 的用药剂量一直受到关注。目前,ACEI/ARB 的应用剂量主要基于其抗高血压效果, 近年来研究表明大剂量 ACEI/ARB 治疗心衰效果明显优于低剂量给药,2016 ESC 心衰治疗指南也推荐应在患者可耐受前提下将 ACEI/ARB 的给药剂量滴定至最大推荐剂量,从而取得最优治疗效果[2]。本课题组前期发表的数据显示超大剂量 ARB(缬沙坦 320～720 mg) 治疗 DCM 合并心衰患者效果比常规剂量更好,可以明显降低全因死亡或再住院率,改善心功能[3],且不增加其副作用。本研究主要观察和比较了超大剂量与常规剂量 ARB 治疗不同年龄 DCM 合并心衰患者的临床疗效和安全性。

1 资料与方法

1.1 临床资料

选择 2012 年 9 月 -2015 年 6 月于西京医院心内科住院治疗的 DCM 合并心力衰竭患者 117 例为研究对象。DCM 诊断标准根据 1995 年中华心血管病学会组织的专题研讨会提出的诊断参考标准进行。纳入标准:①左心衰或全心衰症状和体征;②球形左心运动功能减退伴左心扩大; ③超声心动图示 LVEF＜35%;④NYHA 功能分级 2-4 级;⑤有症状但注册一个月前心功未发生快速恶化者;⑥年龄 30 岁及以下或 60 及以上者。排除标准:①明确因素引起的心力衰竭、冠脉血管造影显示冠脉狭窄者、有心肌梗死或心绞痛病史者、急性或亚急性心肌炎、糖尿病、酗酒或过量使用违禁药物者;②对药物不耐受、收缩压 <90 mmHg、肾动脉狭窄 >50%、妊娠或哺乳期女性、肾功能损害者、高钾血症、严重房室阻滞及其它对生存有影响的并存病;③经心脏再同步化治疗或心脏移植者、已知的对药物不耐受或以前发生过因咳嗽、药物过敏、高钾血症、氮质血症等不良反应而退出试验者。按照入选顺序将所有患者分为 60 岁及以上年龄超大剂量(32 例,老年超大剂量组)及常规剂量(34 例,老年常规剂量组)ARB 治疗组、30 岁及以下年龄超大剂量(24 例,青年超大剂量组)和常规剂量组(27 例,青年常规剂量组)治疗组。

1.2 治疗方法

两组患者入院后均依据患者病情需要给予β- 受体阻滞剂、扩血管、抗凝、利尿、强心、营养心肌、灯盏生脉胶囊(维持血压平稳)等常规治疗。超大剂量组和常规剂量组患者分别逐渐将缬沙坦加至靶剂量 320-720 mg、80-240 mg 后长期维持。

1.3 观察及评价指标

通过门诊、电话及住院等方式进行随访, 记录全因死亡率、心衰再住院率以及左心室射血分数(LVEF)等。

1.4 随访

每位患者接受治疗后出院, 长期坚持按医嘱服用药物,服用期间出现任何不良反应,立即就诊,及时行相关处理。

1.5 统计学处理

采用 sas9.4 软件进行数据处理。计量资料采用 $\bar{x}\pm s$ 表示,两组间比较采用 t 检验;计数资料用百分率表示,两组间比较采用卡方检验等,以 $P<0.05$ 表示为差异有统计学意义。

2 结果

2.1 各组患者基线资料的比较

超大剂量组与常规剂量组、老年超大剂量组与老年常规剂量组年龄、性别、BMI、心率、收缩压、舒张压、心功能各级人数及比例、高血压人数及比例、LVEF 值等均无统计学差异;青年常规剂量组舒张压显著高于青年超大剂量组($P<0.05$),但两组其它各项基线资料均无统计学差异,见表 1-1、1-2 及 1-3。

2.2 各组临床疗效的比较

2.2.1 全因死亡率、心衰再住院率比较 超大剂量组、老年超大剂量组全因死亡率、心衰住院率明显低于其常规剂量组(P<

表 1-1 超大剂量组与常规剂量组基线资料的比较

Table 1-1 Comparison of the baseline data between supramaximal dose group and normal dose group

Clinical baseline data	Supramaximal dose group (n=56)	Normal dose group(n=61)
Male	42(75)	37(61)
Age	51.05± 23.39	57.11± 21.30
BMI(kg/m^2)	21.45± 3.37	23.15± 3.07
Heart rate	82.57± 16.87	80.41± 15.26
Diastolic pressure(mmHg)	71.04± 11.12	73.33± 16.52
Systolic pressure(mmHg)	110.73± 16.57	115.39± 22.23
NYHAⅡ	15(26)	12(20)
NYHAⅢ	23(41)	26(42)
NYHAⅣ	18(32)	23(38)
LVEF(%)	28.77± 5.15	30.39± 7.95
Hypertension	12(21)	15(24)

表 1-2 老年超大剂量组与老年常规剂量组基线资料比较

Table 1-2 Comparison of the baseline data between old supramaximal dose group and old normal dose group

Clinical baseline data	Old supramaximal dose group(n=32)	Old normal dose group(n=34)
Male	24(75)	19(56)
Age	70.72± 4.68	69.00± 6.65
BMI(kg/m^2)	23.12± 3.21	23.64± 2.24
Heart rate	76.94± 14.33	78.29± 14.97
Diastolic pressure(mmHg)	72.03± 10.96	70.18± 12.18
Systolic pressure(mmHg)	113.31± 15.19	113.00± 20.39
NYHAⅡ	6(19)	6(18)
NYHAⅢ	15(47)	14(41)
NYHAⅣ	11(34)	14(41)
LVEF(%)	28.88± 4.13	29.94± 8.08
Hypertension	9(28)	9(26)

表 1-3 青年超大剂量组与青年常规剂量组基线资料比较

Table 1-3 Comparison of the baseline data between yong supramaximal dose group and young normal dose group

Clinical baseline data	Yong supramaximal dose group(n=24)	Young normal dose group(n=27)
Male	18(75)	20(75)
Age	24.83± 4.80	23.42± 6.97
BMI(kg/m^2)	19.42± 2.30	22.19± 4.24
Heart rate	90.50± 17.16	86.42± 15.07
Diastolic pressure(mmHg)	69.71± 11.42	82.25± 23.55[a]
Systolic pressure(mmHg)	107.29± 18.01	122.17± 26.58
NYHAⅡ	9(38)	7(27)
NYHAⅢ	8(33)	12(45)
NYHAⅣ	7(29)	7(27)
LVEF(%)	28.63± 6.34	31.67± 7.77
Hypertension	3(13)	4(17)

Note: Compared with yong supramaximal dose group, *P* [a]*<0.05*.

0.05),见表 2-1、2-2;青年超大剂量组的心衰再住院率显著低于青年常规剂量(*P<0.05*),但两组全因死亡率比较未有明显差异,见表 2-3。

2-1 超大剂量组与常规剂量组全因死亡率、心衰再住院率的比较[例(%)]

Table 2-1 Comparison of the all cause death and hospitalization rate between supramaximal dose group and normal dose group[n(%)]

Groups	Supramaximal dose group (56)	Normal dose group (61)
All-case death	5(9)	17(28)[a]
Hospitaization	6(11)	24(39)[b]

Note: Compared with supramaximal dose group, *P [a]<0.05, P [b]<0.05.*

表 2-2 老年超大剂量组与老年常规剂量组全因死亡率、心衰再住院率的比较[例(%)]

Table 2-2 Comparison of all cause death and hospitalization rate between old supramaximal dose group and old normal dose group[n(%)]

Groups	Old supramaximal dose group(n=32)	Old normal dose group (n=34)
All-case death	4(13)	12(35)[a]
Hospitaization	5(16)	13(38)[b]

Note: Compared with old supramaximal dose group, *P [a]<0.05, P [b]<0.05*.

表 2-3 青年超大剂量组与常规剂量组全因死亡率、心衰再住院率的比较[例(%)]

Table 2-3 Comparison of all cause death and hospitalization rate between yong supramaximal dose group and young normal dose group[n(%)]

Groups	Yong supramaximal dose group(n=24)	Young normal dose group(n=27)
All-case death	1(4)	5(19)
Hospitaization	1(4)	11(41)[a]

Note: Compared with yong supramaximal dose group, *P [a]<0.05.*

2.2.2 LVEF 比较　各组患者治疗后左室射血分数 (LVEF)均较治疗前有明显提高,且超大剂量组、老年超大剂量组、青年超大剂量组的 LVEF 值均显著高于其常规剂量组(*P* 均＜0.05),见表 3-1、3-2、3-3。

2.3 各组不良反应发生情况的比较

所有患者治疗前后均接受包括血尿常规、甲状腺功能、肝功能、肾功能、离子检测,主要不良反应包括低血压、肝功损害、肾功损害,但两组各项不良反应发生率比较差异均无统计学差异：超大剂量组以上各项不良反应分别为 15 例 (27%)、11 例(20%)、14 例(25%);常规剂量分别为 11 例(18%)、10 例(16%)、13 例(21%)。另外,超大剂量组与常规剂量组中均未出现高钾血症,这可能因为实验患者肾功本来就未受严重损害和加入的预防高钾血症的利尿剂。总之,各组患者对药物均耐受良好,超大剂量组与常规剂量组不良反应发生率比较无统计学差异,见表 4。

表 3-1 超大剂量组与常规剂量组 LVEF 值比较[(%)]

Table 3-1 Comparison of the LVEF between supramaximal dose group and normal dose group

Groups	Supramaximal dose group(56)	Normal dose group (61)
Prior treatment	28.77± 5.15	30.39± 7.95
Post treatment	41.65± 7.21	35.15± 7.91[a]

Note: Compared with supramaximal dose group, *P [a]<0.05.*

表 3-2 老年超大剂量组与老年常规剂量组 LVEF 值的比较[(%)]

Table 3-2 Comparison of the LVEF between old supramaximal dose group and old normal dose group

Groups	Old supramaximal dose group(n=32)	Old normal dose group (n=34)
Prior treatment	28.88± 4.13	29.94± 8.08
Post treatment	41.18± 8.78	34.14± 7.34[a]

Note: Compared with old supramaximal dose group, *P [a]<0.05.*

Table 3-3 青年超大剂量组与青年常规剂量组 LVEF 值比较[(%)]

Table 3-3 Comparison of the LVEF between young supramaximal dose group and young normal dose group

Groups	Yong supramaximal dose group(n=24)	Young normal dose group(n=27)
Prior treatment	28.63± 6.34	31.67± 7.77
Post treatment	42.22± 4.77	37.18± 8.96[a]

Note: Compared with yong supramaximal dose group, *P [a]<0.05.*

表 4 超大剂量组与常规剂量组主要不良反应发生率[例(%)]

Table 4 Comparison of the incidence of adverse effect between supramaximal dose group and normal dose group[n(%)]

Groups	Supramaximal dose group(56)	Normal dose group (61)
Liver function disturbance	11(20)	10(16)
Impaired renal function	14(25)	13(21)
Hypotension	15 (27)	11 (18)

3 讨论

心衰发生发展的主要机制是心肌重构,其自发进展的驱动力来自神经内分泌系统和细胞因子,尤其是 RAAS 和交感神经系统长期持续的过度激活[4,5]。据此,抑制 RAAS 是治疗心衰的重要手段。RASS 以自分泌、旁分泌的形式存在于心、肾、脑、血管等多个组织器官[6,7]。在心脏方面,细胞水平上引起正性肌力作用、舒张功能不全;促进肾上腺素分泌引起心律失常;作用于冠状动脉,使其收缩出现心肌缺血,同时也使原癌基因表达,导致心肌肥大、重塑等[8,9]。自上世纪 90 年代开始,与 ACEI/ARB 相关的一系列大样本临床研究已证实这两类药物不仅可以降低心衰患者的病死率、减少住院率,还能延缓和逆转心肌重构[10,11], 这也是历史上首次证实一种药物能够降低心衰患者的病死率并改善预后。然而,仍有很多 DCM 合并心衰患者在接受

规范 ACEI/ARB 治疗的情况下进展至心衰末期,这可能是由于目前推荐的 ACEI/ARB 用量还不能有效阻滞组织中的 RAAS[12],组织 RAAS 过度激活参与心肌细胞肥大、纤维化及最终的心室重塑。目前应用的 ACEI/ARB 剂量主要是基于其抗高血压作用[12]。已有大量研究表明,大剂量 ACEI/ARB 治疗心衰效果明显优于低剂量:依那普利 40 mg/d[13]、卡托普利≥ 75 mg/d[14]、赖诺普利 32.5-35 mg/d [15](ATLAS 试验)、洛沙坦 150 mg/d[16](ATLAS 研究)均改善心衰患者了流动力学、提高运动耐量,并减少了住院需求。这些结果均提示心衰患者应用超过 A-CEI/ARB 抗高血压的最大推荐剂量(超大剂量)可能发挥更强的心血管保护作用[17]。

我们前期的研究表明超大剂量 ARB 治疗心衰效果明显优于常规剂量,能显著降低全因死亡或心衰入院率,并更大程度上改善心功能[3]。另外,我们还发现超大剂量 ARB 疗效优于超大剂量 ACEI,该现象可能与 ARB 组织穿透力强和脂溶性强有关系[18],或者 ARB 直接拮抗血管紧张素Ⅱ受体,不发生 "ACE 逃逸现象 "[19,20],故本研究直接给予 DCM 合并心衰患者 ARB 治疗。本研究结果进一步证实长期应用超大剂量 ARB 治疗 DCM 合并心衰患者能显著降低其全因死亡率和心衰再住院率,且能更大程度改善心功能。这些结果均提示目前指南推荐的 ARB 治疗剂量对阻止心脏重塑和心衰进程还不足够。用超大剂量 ARB 治疗 DCM 心衰患者,使其通过抑制体内 RAAS 所达到的心肌保护作用达到最优,在治疗中显示出强力抑制 RAAS 的优势,很可能会取得更好的疗效。

鉴于不同年龄心衰患者体内 RAAS 激活程度不同,RAAS 抑制剂的治疗效果会产生一定差异。本研究分别在老年和青年 DCM 合并心衰患者中对不同剂量 ARB 的疗效进行了观察和比较。在老年患者中,超大剂量 ARB 治疗更明显地降低了全因死亡率和心衰住院率,并更大程度上改善了心功能;而在青年患者中,超大剂量 ARB 治疗降低了心衰再住院率,但未能降低全因死亡率。这可能是由于 RAAS 在青年心衰患者体内激活程度相对较低。但本研究样本量较小,此问题仍需进一步进行大样本量研究。

目前,不推荐超大剂量 ARB 的主要原因是其给药后引起的包括低血压、肝肾功损害、高钾血症等不良反应[21]。但本研究及课题组前期发表的数据均表明超大剂量贝那普利(40-80 mg/d) 或缬沙坦(320-640 mg/d)治疗后患者耐受良好,且在院内监护下和适当管理的情况下七天内快速加量至靶剂量安全可行,推荐睡前给药及中药(黄芩素和人参皂苷为主要活性成分)以防止低血压相关症状出现。

总之,本研究结果表明长期超大剂量 ARB 治疗 DCM 心衰患者能显著降低其全因死亡率和心衰再住院率,并更大程度改善心功能。同时,超大剂量 ARB 治疗老年 DCM 合并心衰患者的疗效与此相似;但超大剂量 ARB 治疗青年 DCM 合并心衰患者仅能降低心衰住院率,不能降低全因死亡率。

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