· 临床研究 ·

慢性心力衰竭合并 2 型糖尿病对老年人认知功能水平的影响

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【摘 要】 **目的** 探讨慢性心力衰竭(CHF)合并 2 型糖尿病(T2DM)对老年人认知功能的影响。**方法** 选取 2019 年 10 月至 2020 年 5 月江苏省荣军医院住院康复及无锡市梁溪区家庭康复的老年 CHF 和(或)T2DM 患者 116 例。根据是否合并 CHF 及 T2DM 分成 3 组:CHF 组(n=47)、T2DM 组(n=29)及 CHF 合并 T2DM 组(n=40)。收集患者一般资料。采用蒙特利尔认知评估量表(MoCA)评估患者认知功能,根据 MoCA 总评分< 26 分为认知功能障碍(CI),将 116 例老年患者分为 CI 组(n=55)和非认知功能障碍(NCI)组(n=61)。采用 SPSS 25.0 软件进行统计分析。采用 logistic 回归分析 CHF 合并 T2DM 患者发生 CI 的影响因素。**结果** 与 CHF 组及 T2DM 组相比,CHF 合并 T2DM 组患者 MoCA 评分显著降低,CI 发生率显著增高,差异均有统计学意义(P<0.05)。与 NCI 组相比,CI 组患者左心室射血分数(LVEF)显著降低,吸烟、CHF 病程、T2DM 病程、痴呆家族史、CHF 家族史、T2DM 家族史、合并高血压、合并房颤、收缩压、糖化血红蛋白(HbA1c)、尿素氮、N 末端脑钠肽前体(NT-proBNP)、汉密尔顿焦虑量表评分及匹兹堡睡眠指数量表评分显著增高,差异均有统计学意义(P<0.05)。多因素 logistic 回归分析显示,CHF 病程、痴呆家族史、合并房颤、HbA1c、NT-proBNP、LVEF 是 CHF 合并 T2DM 患者发生 CI 的独立危险因素(均 P<0.05)。**结论** 与单纯 T2DM 及单纯 CHF 患者相比,CHF 合并 T2DM 会加重老年人 CI。

【关键词】 老年人;糖尿病, 2 型;慢性心力衰竭;认知功能
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Effect of chronic heart failure with comorbid type 2 diabetes mellitus on cognitive function of the elderly

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【**Abstract**】 **Objective** To investigate the effects of chronic heart failure (CHF) with comorbid type 2 diabetes mellitus (T2DM) on cognitive function in elderly. **Methods** A total of 116 elderly patients with CFH and (or) T2DM were selected, who underwent inpatient rehabilitation in Jiangsu Rongjun Hospital and home-based rehabilitation in Liangxi District of Wuxi City from October 2019 to May 2020. They were divided into three groups according to the comorbidity of CHF and T2DM: CHF group (n=47), T2DM group (n=29), and CHF-T2DM group (n=40). General data of the patients were collected, and their cognitive function was assessed using the Montreal Cognitive Assessment Scale (MoCA). Based on MoCA score (< 26), the included 116 patients were classified as having cognitive impairment (CI, n=55) and having no cognitive impairment (NCI, n=61). Statistical analyses were performed using SPSS statistics 25.0. Logistic regression was used to analyze the affecting factors of CI in CHF patients with comorbid T2DM. **Results** The CHF-T2DM group had a significantly lower MoCA score and a significantly higher incidence of CI than the CHF and T2DM groups (P<0.05 for both). The CI group had significantly lower left ventricular ejection fraction (LVEF) and significantly higher score than the NCI group in smoking, course of CHF and T2DM, family history of dementia, CHF and T2DM, comorbid hypertension, comorbid atrial fibrillation, systolic blood pressure, glycosylated hemoglobin Alc (HbA1c), urea nitrogen, NT-proBNP, Hamilton depression scale score, and Pittsburgh sleep quality index score (all P<0.05). Multivariate logistic regression analysis showed that course of CHF, family history of dementia, comorbid atrial fibrillation, glycated hemoglobin, amino terminal pro-brain natriuretic peptide, and left ventricular ejection fraction were independent risk factors for the development of CI in CHF patients with T2DM (P<0.05 for all). **Conclusion** Compared with T2DM alone and CHF alone, CHF with comorbid T2DM would aggravate CI in the elderly.

【**Key words**】 aged; diabetes mellitus, type 2; chronic heart failure; cognitive function

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慢性心力衰竭(chronic heart failure,CHF)是各类心血管疾病发展的最后阶段,主要是由于心脏泵血功能障碍所致[1]。全球CHF患者的数量正快速增长,目前国内有450万CHF患者[2],美国CHF患者数量更是高达650万[3]。越来越多的研究证实CHF患者更易发生认知功能障碍(cognitive impairment,CI),CI会显著降低CHF患者的执行能力,导致患者治疗的依从性降低,生活自理能力下降,再入院率和死亡率增加[4,5]。有研究发现糖尿病(diabetes mellitus,DM)可能是CI的独立危险因素[6],且DM在发生CI的CHF患者中尤其常见,提示DM可能会进一步增加CHF患者CI的发生。但目前关于CHF合并2型糖尿病(type 2 diabetes mellitus,T2DM)对老年人认知功能影响的研究较少,本研究探讨了合并T2DM的老年CHF患者认知功能情况及相关影响因素,以便临床早期阻断CI的继续发展,提高老年群体的生命质量。

1 对象与方法

1.1 研究对象

选取2019年10月至2020年5月江苏省荣军医院住院康复及无锡市梁溪区接受家庭康复的老年CHF和(或)T2DM患者116例。纳入标准:(1)CHF的诊断符合《中华心血管病杂志》编辑委员会于2018年发布的中国心力衰竭诊断和治疗指南[7]中的诊断标准;(2)T2DM诊断符合中华医学会糖尿病学分会于2018年发布的中国2型糖尿病防治指南[8]中的诊断标准,病情稳定,无明显并发症,近3个月血糖控制平稳,糖化血红蛋白(glycosylated hemoglobin Alc,HbA1c)在正常范围;(3)初中以上文化,知情同意,志愿参加。排除标准:(1)入组前6个月内有急性心、脑血管意外事件发生;(2)包括痴呆在内的可能影响认知功能的神经系统疾病;(3)严重的精神疾病;(4)精神活性物质成瘾;(5)可能影响认知功能的全身性疾病;(6)心脏瓣膜病及心肌病。

1.2 方法

1.2.1 资料收集 收集患者年龄、性别、体质量指数(body mass index ,BMI)、社会支持情况、情绪、睡眠、既往病史、吸烟、家族史、生化指标、6分钟步行试验(six-minute walk test,6MWT)、左心室射血分数(left ventricular ejection fraction,LVEF)等情况。

1.2.2 功能评分 采用蒙特利尔认知评估量表(Montreal cognitive assessment,MoCA)[9]评定患者的认知功能,该量表总评分为30分,总评分≥26分时评定为认知功能正常,总评分< 26分时评定为CI,当受教育年限≤12年时,需在MoCA评分基础上加1分。采用汉密尔顿焦虑量表(Hamilton anxiety scale,HAMA)评估焦虑情绪,总评分<7分时无焦虑症状。采用汉密尔顿抑郁量表(Hamilton depression scale,HAMD)评估抑郁情绪,总评分<8分时无抑郁。采用匹兹堡睡眠质量指数量表(Pittsburgh sleep quality index,PSQI)评估睡眠质量,总评分越高表示睡眠质量越差。采用社会支持评定量表(social support rating scale,SSRS)[10]评估社会支持情况,总评分越高则支持越好[10]。

1.2.3 分组 根据是否合并CHF及T2DM将入组患者分为3组:CHF组47例、T2DM组29例及CHF合并T2DM组40例。根据MoCA评分将患者分为CI组55例及非认知功能障碍组(non-cognitive impairment, NCI)61例。

1.3 统计学处理

采用SPSS 22.0软件进行统计分析。计量资料以均数±标准差($\bar{x}\pm s$)表示,2组间比较采用t检验;3组间比较采用方差分析,组间两两比较采用LSD-t检验,计数资料以例数(百分率)表示,组间比较采用χ^2检验。采用logistic回归分析CHF合并T2DM患者发生CI的影响因素。$P<0.05$为差异有统计学意义。

2 结 果

2.1 3组患者MoCA评分及CI发生率比较

与CHF组及T2DM组患者比较,CHF合并T2DM组MoCA评分显著降低,CI发生率显著增高(均$P<0.05$)。与T2DM组比较,CHF组患者CI发生率显著增高,差异有统计学意义($P<0.05$;表1)。

2.2 CI组与NCI组患者一般资料比较

与NCI组患者比较,CI组LVEF显著降低,吸烟、CHF病程、T2DM病程、痴呆家族史、CHF家族史、T2DM家族史、合并高血压、合并房颤、收缩压、HbA1c、尿素氮、N末端脑钠肽前体(NT-terminal pro-brain natriuretic peptide, NT-proBNP)及PSQI评分显著增高(均$P<0.05$;表2)。

表 1 3 组患者 MoCA 评分及 CI 发生率比较

Table 1 Comparison of MoCA score and CI incidence among three groups

Group	n	MoCA (points, $\bar{x}\pm s$)	Incidence of CI [n(%)]
CHF	47	25.23±1.40	21(44.68)$^{\#}$
T2DM	29	25.86±1.54	8(27.59)
CHF combined with T2DM	40	22.95±2.86$^{*\#}$	26(65.00)$^{*\#}$

MoCA: Montreal cognitive assessment; CI: cognitive impairment; CHF: chronic heart failure; T2DM: type 2 diabetes mellitus. Compared with CHF group, $^{*}P<0.05$; compared with T2DM group, $^{\#}P<0.05$.

2.3 CHF 合并 T2DM 患者发生 CI 的多因素 logistic 回归分析

以老年人认知功能是否发生障碍为因变量,将单因素分析中有意义的吸烟史、CHF 病程、T2DM 病程、痴呆家族史、CHF 家族史、T2DM 家族史、合并高血压、合并房颤、收缩压、HbA1c、尿素氮、NT-proBNP、LVEF、HAMD 评分及 PSQI 评分作为自变量,进行多因素 logistic 回归分析。结果显示,CHF 病程、痴呆家族史、合并房颤、HbA1c、NT-proBNP 及 LVEF 是 CHF 合并 T2DM 患者发生 CI 的独立危险因素(均 $P<0.05$;表 3)。

表 2 CI 组与 NCI 组患者一般资料比较

Table 2 Comparison of general information between CI group and NCI group

Item	CI group (n=55)	NCI group (n=61)	χ^2/t	P value
Age(years, $\bar{x}\pm s$)	83.02±6.98	82.46±7.53	0.410	0.290
Male[n(%)]	27(49.09)	34(55.74)	0.982	0.322
Monthly income(yuan, $\bar{x}\pm s$)	0.50±0.17	0.52±0.15	0.690	0.490
Schooling(years, $\bar{x}\pm s$)	10.18±1.23	10.25±1.09	0.301	0.770
Smoking[n(%)]	43(78.18)	35(57.38)	10.051	0.002
Course of CHF(years, $\bar{x}\pm s$)	12.62±2.16	11.26±2.66	2.991	<0.001
Course of T2DM(years, $\bar{x}\pm s$)	11.74±2.55	8.71±2.07	5.410	<0.001
Family history of dementia[n(%)]	36(65.45)	20(32.79)	4.143	<0.001
Family history of CHF[n(%)]	30(54.55)	19(31.15)	1.076	<0.001
Family history of T2DM[n(%)]	33(60.00)	28(45.90)	3.934	0.047
Coronary heart disease[n(%)]	34(61.82)	30(49.18)	3.420	0.060
Hypertension[n(%)]	49(89.09)	35(57.38)	25.977	<0.001
Atrial fibrillation[n(%)]	20(36.36)	14(22.95)	4.061	0.040
BMI(kg/m^2, $\bar{x}\pm s$)	22.92±1.23	22.73±1.42	0.750	0.451
Systolic blood pressure(mmHg, $\bar{x}\pm s$)	134.45±9.01	130.25±10.06	2.361	0.020
Diastolic blood pressure(mmHg, $\bar{x}\pm s$)	74.15±8.36	73.55±7.78	0.690	0.490
FBG(mmol/L, $\bar{x}\pm s$)	5.58±1.23	5.53±1.09	0.250	0.811
HbA1c(%, $\bar{x}\pm s$)	6.16±1.27	5.64±1.42	2.061	0.040
Hemoglobin(g/L, $\bar{x}\pm s$)	111.47±12.60	111.56±13.59	0.030	0.971
Triglyceride(mmol/L, $\bar{x}\pm s$)	1.26±0.61	1.28±0.46	0.201	0.851
Total cholesterol(mmol/L, $\bar{x}\pm s$)	4.13±1.14	3.92±0.81	1.130	0.260
ALT(U/L, $\bar{x}\pm s$)	20.48±11.51	21.96±15.75	1.571	0.590
AST(U/L, $\bar{x}\pm s$)	23.82±10.44	26.70±16.35	1.121	0.270
Urea nitrogen(mmol/L, $\bar{x}\pm s$)	5.76±2.96	4.84±1.65	2.080	0.041
Creatinine(μmol/L, $\bar{x}\pm s$)	71.44±24.89	76.60±23.67	1.145	0.260
NT-proBNP(pg/ml, $\bar{x}\pm s$)	1 326.51±121.64	965.00±154.69	3.350	<0.001
6MWT(m, $\bar{x}\pm s$)	392.84±55.08	399.46±53.80	0.651	0.510
LVEF(%, $\bar{x}\pm s$)	49.16±6.22	52.59±6.87	2.813	0.012
HAMA(points, $\bar{x}\pm s$)	17.07±2.43	16.92±2.79	0.320	0.275
HAMD(points, $\bar{x}\pm s$)	19.33±2.53	17.74±2.91	3.111	<0.001
PSQI(points, $\bar{x}\pm s$)	10.04±3.32	8.54±2.92	2.580	0.013
SSRS(points, $\bar{x}\pm s$)	34.49±2.64	35.31±3.71	1.362	0.181

CI: cognitive impairment; NCI: non-cognitive impairment; CHF: chronic heart failure; T2DM: type 2 diabetes mellitus; BMI: body mass index; FBG: fasting blood glucose; HbA1c: glycosylated hemoglobin Alc; ALT: alanine aminotransferase; ATS: glutamic oxaloacetic transaminase; NT-proBNP: N-terminal pro-brain natriuretic peptide; 6MWT: six-minute walk test; LVEF: left ventricular ejection fraction; HAMA: Hamilton anxiety scale; HAMD: Hamilton depression scale; PSQI: Pittsburgh sleep quality index; SSRS: social support rating scale. 1 mmHg=0.133 kPa.

表3 CHF合并T2DM患者发生CI的多因素logistic回归分析

Table 3 Multivariate logistic regression analysis of CI in CHF patients with T2DM

Item	*B*	*SE*	*Wald* χ^2	*P* value	*OR*	95% *CI*
Course of CHF	2.071	0.431	2.275	0.007	2.573	1.620-20.043
Family history of dementia	1.037	0.667	4.479	<0.001	3.715	1.229-5.152
Atrial fibrillation	2.031	0.773	5.678	0.002	2.432	0.342-3.787
HbA1c	1.993	0.304	5.771	0.013	1.948	1.871-6.755
NT-proBNP	1.852	0.737	6.081	<0.001	3.591	1.508-9.803
LVEF	1.553	0.551	3.308	0.017	1.213	1.012-4.706

CHF: chronic heart failure; T2DM: type 2 diabetes mellitus; CI:cognitive impairment; HbA1c: glycosylated hemoglobin Alc; NT-proBNP: N-terminal pro-brain natriuretic peptide; LVEF: left ventricular ejection fraction.

3 讨 论

老年CHF患者心脏泵血功能障碍引起的脑血流灌注不足,可能直接导致CI[11],主要以执行能力、记忆力、语言、注意力等方面的障碍为主[12]。心力衰竭发生后,肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system,RAAS)的激活及各种炎性因子的作用,会使海马功能受到影响[13],加速脑内Aβ淀粉样蛋白沉积[14,15],进一步加速CI的进展。此外,载脂蛋白E基因也是导致CHF患者发生脑功能代谢失调的重要机制[16]。近年来,有国内研究显示,CHF患者CI的发病率较高,心功能受损可能是加重认知功能下降的一个重要因素,尤其是LVEF能够作为独立因素对CHF患者的认知功能产生影响[17,18],与本研究结果基本一致。本研究发现,CI患者的CHF病程更长、CHF家族史更多。多因素logistic回归分析显示,LVEF和NT-proBNP是CHF合并T2DM患者发生CI的独立危险因素。LVEF能够客观反映心脏功能状态,NT-proBNP更是目前反映心功能的金标准,提示老年群体的认知功能与心功能水平密切相关。

T2DM为CI的一个重要危险因素,可引起患者记忆力、注意力及计算力下降[19]。胰岛素抵抗是T2DM的一个重要发病机制。国外有研究报道,胰岛素抵抗时,会使执行能力下降,海马体积缩小[20]。有动物研究发现,胰岛素抵抗会减弱糖原合成酶激酶3的磷酸化作用,加速β淀粉样蛋白的成熟生成,促进Tau蛋白的磷酸化,导致出现与老年性痴呆相似的病理表现[21]。当T2DM患者血糖控制欠佳,脑组织内血糖长期处于高水平时,会引起过量山梨醇堆积,增加晚期糖基化终末产物(advanced glycation end products,AGEs)的产量,AGEs能直接损伤血管内皮功能,进而破坏微小血管及神经元功能[22],引起血浆黏稠度增加和脑血栓形成,降低脑血流量,造成神经必需营养物质的不足,直接导致CI的发生[23,24]。本研究发现,CI组较NCI组患者T2DM病程更长、家族史更多。进行多因素logistic回归分析后发现,HbA1c是CI的独立危险因素。HbA1c是目前反映T2DM长期血糖监控的金标准,提示T2DM的血糖控制情况与CI的发病显著相关。

T2DM是CHF的主要合并症之一。既往研究显示,T2DM与CHF患者CI的发生独立相关[25]。本研究发现,与单纯CHF患者相比,CHF合并T2DM患者的MoCA评分显著降低,CI的发病率显著增高。对于CHF患者而言,T2DM可通过RAAS系统和下丘脑-垂体-肾上腺轴(hypothalamis-pituitary-adrenal axis,HPA)的作用促进CI发生。T2DM所致的高血糖会促进RAAS系统激活,上调血管紧张素Ⅱ受体水平,激活细胞氧化应激机制,诱导Fos基因的表达,加速神经细胞凋亡[26]。T2DM会促使CHF患者HPA功能更亢进,引起皮质醇浓度上升,形成活性氧簇,在海马组织内发生氧化损伤,促进神经细胞凋亡[27]。

综上,老年CHF患者合并T2DM会进一步加重CI。启示我们,临床中要关注心功能及血糖水平对老年人认知功能的影响,对于合并T2DM的老年CHF患者,为了减缓认知功能损伤,应该更加重视T2DM的防治,密切监测患者血糖,尤其是对HbA1c的监控。本研究样本量较小,有待进一步大样本多中心的研究加以证实。

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致“一带一路”沿线国家和地区医学机构

《中华老年多器官疾病杂志》是由中国工程院院士、老年心脏学专家王士雯教授于2002年创办的全世界惟一一本以老年心脏病和老年心脏病合并其他器官疾病为主要内容的杂志,月刊,由中国人民解放军总医院老年心血管病研究所主办。杂志已被“中国科技论文统计源期刊”(中国科技核心期刊)收录。本杂志的摘要、图表和参考文献,均为中、英文双语对照,方便国外读者顺利阅读。为促进中国与“一带一路”沿线国家和地区的医学及文化交流,本刊将免费刊登其来稿,并赠送当期杂志。欢迎“一带一路”沿线国家和地区的老年心脏病和老年病学医生、学者踊跃投稿。

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The Chinese Journal of Multiple Organ Diseases in the Elderly (*Zhonghua Laonian Duoqiguan Jibing Zazhi*) is founded in 2002 by Shiwen Wang, Member of Chinese Academy of Engineering, a renowned geriatric cardiologist in China. The journal is published monthly by the Institute of Geriatric Cardiology (IGC), Chinese PLA General Hospital in Beijing, China. The journal, the only one in the world currently, focuses on both basic research and clinical practice to the diagnosis and treatment of cardiovascular disease in the aged people, especially those with concomitant disease of other major organ-systems, like the lungs, kidneys, liver, central nervous system, gastrointestinal tract or endocrinology, *etc*. The journal has been listed in the most authoritative Chinese database, the Chinese Scientific and Technical Papers and Citations Database (Chinese Core Sci-Tech Periodical). For convenience of foreign readers, the main parts of the paper, including abstract, tables, figures and references, are expressed in Chinese-English bilingually. To facilitate the cultural and academic communication between China and countries or regions along the Belt and Road, the journal welcomes the manuscripts from these areas. If reviewed qualified, the manuscript would be published without charging, and the authors would receive a complimentary copy of the current issue.

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