

doi: 10.13241/j.cnki.pmb.2020.08.013

肥厚型心肌病患者认知功能障碍的发生及影响因素分析 *

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摘要 目的: 探讨肥厚型心肌病(HCM)患者认知功能障碍的发生及影响因素。**方法:** 收集 2018 年 4 月至 2019 年 7 月期间空军军医大学第一附属医院超声医学科 HCM 患者 198 例。综合北京版蒙特利尔认知评估(MoCA)量表结果及教育程度,判断患者认知功能:文盲且 MoCA 得分<14 分、1 年≤教育年限≤6 年且 MoCA 得分<20 分、或教育年限>6 年且 MoCA 得分<25 分为认知功能障碍组(n=37),其余为认知功能正常组(n=161)。比较两组患者一般资料、超声心动图检查结果及认知功能评估结果。采用多因素 logistic 回归分析筛选 HCM 患者认知功能障碍的可能危险因素。**结果:** HCM 患者认知功能障碍的发生率为 18.7%(37/198)。与认知功能正常组相比,认知功能障碍组 HCM 患者年龄较大($P<0.05$),受教育年限较短($P<0.05$),心功能分级及左心室舒张功能较差($P<0.05$),激发左心室流出道压差较高($P<0.05$)。认知功能障碍组 HCM 患者 MoCA 得分较低($P<0.05$),尤其在视空间与执行功能和延迟回忆($P<0.05$)两项上得分较差。多因素 logistic 回归分析结果表明,调整年龄(OR=14.435, 95 %CI: 4.476-46.550; $P<0.001$)和教育年限(OR=5.274, 95 %CI: 2.024-13.744; $P=0.001$)后,激发左心室流出道压差(OR=3.844, 95 %CI: 1.551-9.524; $P=0.004$)是 HCM 患者认知功能障碍的独立危险因素。**结论:** 激发左心室流出道压差可以增加 HCM 患者认知功能障碍的发生风险。

关键词: 肥厚型心肌病; 认知功能障碍; 激发左心室流出道压差**中图分类号:** R542.2 **文献标识码:** A **文章编号:** 1673-6273(2020)08-1462-06

Occurrence and Influencing Factors Associated with Cognitive Impairment in Patients with Hypertrophic Cardiomyopathy*

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ABSTRACT Objective: To describe the occurrence of cognitive impairment in hypertrophic cardiomyopathy (HCM) patients and explore possible influencing factors associated with cognitive impairment. **Methods:** 198 patients with HCM, who were admitted in the department of ultrasound, Xijing Hospital of Air Force Medical University from April 2018 to July 2019, were collected. Both Montreal Cognitive Assessment (MoCA) test and education years were considered to assess cognitive function of these patients. The cutoff score for cognitive impairment to the present study were 14 for illiterate patients, 19 for patients with 1-6 years of education, and 24 for patients with 7 or more years of education. And according to this criterion, HCM patients were divided into cognitive impairment group (n=37) and normal cognitive function group (n=161). Demographic data and clinical characteristics, life style and history of diseases, echocardiography and cognitive assessment were collected and compared between two groups. Multivariate logistic regression analysis was used to assess the possible risk factors for cognitive impairment in HCM patients. **Results:** The incidence of cognitive impairment in HCM patients was 18.7 %. Patients in cognitive impairment group were older in age ($P<0.05$), had shorter years of education ($P<0.05$), poorer cardiac function and diastolic function in left ventricular ($P<0.05$) and significantly higher pressure of provoked left ventricular outflow tract pressure gradient (LVOT-PG, $P<0.05$). Besides, patients in cognitive impairment group had lower MoCA score ($P<0.05$), especially a poorer performance in visual space and executive function and delayed recall ($P<0.05$). The results of multivariate logistic regression analysis showed that after adjusting for age (OR=14.435, 95 %OR 4.476-46.550; $P<0.001$) and years of education (OR=5.274,

* 基金项目: 国家科技部国际合作专项(2014DFA31980); 国家自然科学基金项目(81471197; 81601498; 81901755);

陕西省重点科研项目(2017ZDXM-SF-058); 陕西省重点研发项目(2019KW-076); 西京医院新技术、新业务资助项目(417432A);

陕西省重点科技创新项目(2014KCT-20)

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(收稿日期: 2019-12-14 接受日期: 2020-01-10)

95 %OR 2.024-13.744; $P=0.001$), LVOT-PG (OR=3.844, 95 %CI: 1.551-9.524; $P=0.004$) was an independent risk factor for cognitive impairment in HCM patients. **Conclusion:** LVOT-PG can increase the risk of cognitive impairment in patients with HCM. In the clinic, it is necessary to pay attention to the change of LVOT-PG in HCM patients for early prevention of the occurrence and progression of cognitive impairment.

Key words: Hypertrophic cardiomyopathy; Cognitive impairment; Provoked left ventricular outflow tract pressure gradient

Chinese Library Classification (CLC): R542.2 **Document code:** A

Article ID: 1673-6273(2020)08-1462-06

前言

肥厚型心肌病(hypertrophic cardiomyopathy, HCM)是一类常见的遗传性心血管疾病,其在人群中的发病率为1:500-1:200^[1,2]。HCM主要的病理生理学表现为心室壁非对称性肥厚、左心室流出道梗阻和左心室舒张功能障碍^[3],而左心室流出道梗阻通常导致心肌缺血及心输出量的减少^[4]。有研究发现,心输出量下降^[5,6]和左心室舒张功能障碍^[7,8]与认知功能障碍相关。其机制可能为相关脑区血流量减少^[9]、脑血流自动调节功能受损及脑血管反应性减低^[10]等。HCM患者常伴有左心室舒张功能障碍^[11,12],静息及运动状态下心输出量较正常人减低^[13],这能否导致其认知功能发生改变,目前尚无研究报道。本研究的主要目的,探讨HCM患者的认知功能情况,分析HCM患者认知功能障碍可能的影响因素,为预防HCM患者认知功能障碍发生发展提供临床参考依据。

1 资料与方法

1.1 研究对象

收集2018年4月至2019年7月空军军医大学第一附属医院超声医学科HCM患者198例。其中,男性128例,女性70例;年龄20-74岁,平均 (46.16 ± 12.48) 岁。纳入标准:参照2014年欧洲心脏病学会指南中HCM的诊断指南^[14]。排除标准:(1)既往有引起认知功能改变的疾病,如脑部病变、心身疾病、肺部疾病等;(2)已接受过外科室间隔旋切术或酒精消融术治疗的患者;(3)不愿意接受问卷及无法完成问卷的患者。

1.2 研究方法

1.2.1 一般资料收集 综合临床医生问诊及问卷调查,收集患者的基线资料,包括体重指数(body mass index, BMI)、教育年限,检查当日的收缩压和舒张压,纽约心脏病协会(New York Heart Association, NYHA)心功能分级,有无高血压、糖尿病、冠心病,有无晕厥史、猝死家族史、吸烟史和饮酒史等,是否发生过房颤及是否植入起搏器。

1.2.2 临床资料收集 采用Philips EPIQ 7C超声诊断仪。根据指南^[15]测量左心房前后径(left atrial diameter, LAD)及室间隔厚度(interventricular septum, IVS),用双平面Simpson法测量左室射血分数(left ventricular ejection fraction, LVEF)。测量静息状态下左心室流出道压差(left ventricular outflow tract gradient, LVOT-G)、Valsalva动作或下蹲动作后左心室流出道压差(激发左心室流出道压差,provoked left ventricular outflow tract gradient, LVOT-PG),LVOT-G ≥ 30 mmHg认为存在左心室流出道梗阻。测量二尖瓣口舒张早期峰值流速(E),以组织多普勒模式测量二尖瓣环舒张早期峰值速度(e'),使用E/e'评价

左室舒张功能。M超测量是否存在收缩期二尖瓣前向运动(SAM征)。

1.2.3 认知功能评估及分组 采用北京版蒙特利尔认知评估(Montreal Cognitive Assessment, MoCA)量表分别从视空间与执行功能、命名、注意、语言、抽象、记忆力和定向力对患者进行认知功能评估。若患者受教育年限 ≤ 12 年,则总分加1分,总分为30分。量表推荐的最佳截断值为25/26分^[16],该截断值特异性较差^[17,18]。本研究综合教育程度及MoCA得分判断患者认知功能障碍:文盲且MoCA得分 <14 分、1年 $\leq$ 教育年限 ≤ 6 年且MoCA得分 <20 分、或教育年限 >6 年且MoCA得分 <25 分^[19,20]的患者为认知功能障碍组,其余患者为认知功能正常组。

1.3 统计学分析

应用SPSS 20.0软件对数据进行分析。符合正态分布的计量资料采用 $\bar{x} \pm s$ 表示,不符合正态分布的计量资料采用四分位数间距(P25, P75)表示,组间比较采用独立样本t检验或采用Mann-Whitney U检验。计数资料用例(%)表示,组间比较用 χ^2 检验。采用受试者工作特征(receiver operating characteristic curve, ROC)曲线筛选预测认知功能障碍的最适截点值。多因素logistic回归分析HCM患者认知功能障碍的危险因素。 $P < 0.05$ 为有统计学意义。

2 结果

2.1 两组患者临床资料比较

认知功能障碍组患者37例,认知功能正常组患者161例,HCM患者认知功能障碍的发生率为18.7%(37/198)。与认知功能正常组相比,认知功能障碍组患者年龄大($P < 0.05$),受教育年限低($P < 0.05$);认知功能障碍组和认知功能正常组NYHA分级分布不同($P < 0.05$),其中认知功能障碍组II级和III级比例高于认知功能正常组,I级比例低于认知功能正常组;与认知功能正常组相比,认知功能障碍组E/e'显著增高($P < 0.05$),LVOT-PG显著增高($P < 0.05$)。见表1。

2.2 两组患者认知功能比较

与认知功能正常组相比,认知功能障碍组患者MoCA得分较低($P < 0.05$),尤其在视空间与执行功能($P < 0.05$)和延迟回忆($P < 0.05$)两项上得分较差。见表2。

2.3 预测HCM认知功能障碍的ROC曲线分析

ROC曲线分析显示,年龄、NYHA分级、E/e'、LVOT-PG以及教育年限对HCM患者认知功能障碍具有一定的预测价值。其预测曲线下面积、敏感性以及特异性见表3和图1。

2.4 logistic回归分析HCM认知功能障碍的危险因素

单因素logistic回归分析结果显示,年龄、NYHA分级、LVOT-PG、教育年限具有统计学意义。多因素logistic回归分析

结果显示,年龄(OR=14.435, 95 %CI 4.476-46.550; $P<0.001$)、教育年限(OR=5.274, 95 %CI: 2.024-13.744; $P=0.001$)和LVOT-PG (OR= 3.844, 95 %CI: 1.551-9.524; $P=0.004$) 为 HCM 患者认知功能障碍的独立危险因素(表 4)。

表 1 两组患者临床资料比较
Table 1 Comparison of the clinical information between two groups

Project	Cognitive impairment group n=37	Normal cognitive function group n=161	$t/Z/\chi^2$	P
Man	19 (51.4)	109 (67.7)	3.519	0.061
Age (years)	54.05± 9.41	44.34± 12.41	-4.350	<0.001
BMI (Kg/m ²)	24.70± 3.10	24.27± 4.92	0.057	0.612
SBP (mmHg)	122.16± 17.16	123.96± 18.95	-0.530	0.597
DBP (mmHg)	71.86± 10.11	74.19± 12.85	-1.027	0.305
Hypertension	12 (32.4)	48 (29.8)	0.098	0.755
Diabetes mellitus	3 (8.1)	4 (2.5)	2.790	0.123
Coronary artery disease	3 (9.4)	7 (4.9)	0.953	0.394
Atrial fibrillation	3(8.1)	4(2.5)	2.790	0.123
ICD implantation	0(0)	4(2.5)	0.938	1.000
History of syncope	6 (16.2)	22 (13.7)	0.161	0.688
Family history of SCD	5 (13.5)	12 (7.5)	1.408	0.324
Smoke	11 (34.4)	71 (50.0)	2.559	0.110
Drink	11 (34.4)	47 (32.9)	0.027	0.870
NYHA class				
Class I	9(24.3)	83(51.9)	9.169	0.010
Class II	18(48.6)	50(31.2)		
Class III	10(27)	27(16.9)		
Yeats of education (years)	8.54± 5.19	11.58± 4.11	-3.539	<0.001
Echocardiogram				
LAD (mm)	42.24± 8.36	39.74± 6.70	1.953	0.052
LVEF	57.97± 2.94	58.62± 4.30	-0.870	0.386
E/e'	16.56± 5.99	14.46± 5.20	2.069	0.040
IVS (mm)	22.57± 4.29	22.76± 5.19	-0.205	0.838
LVOTO	17(45.9)	56(34.8)	1.611	0.204
LVOT-G (mmHg)	23(6, 89)	12(5, 46)	-1.549	0.219
LVOT-PG (mmHg)	57(7, 106)	13(6, 54)	-2.913	0.013
SAM	20(54.1)	81(50.9)	0.116	0.733

Note: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ICD: implantable cardioverter defibrillator; SCD: sudden cardiac death; NYHA: New York Heart Association functional class; LAD: size of left atrial; LVEF: left ventricular ejection fraction; E/e': ratio of the early diastolic peak velocities of mitral inflow and mitral annulus; IVS: interventricular septum thickness; LVOTO: left ventricular outflow tract obstruction; LVOT-G: left ventricular outflow tract pressure gradient; LVOT-PG: provoked left ventricular outflow tract pressure gradient; SAM: systolic anterior motion

3 讨论

认知功能障碍可降低患者的生活质量, 导致其医从性下降,一定程度上影响疾病的发展和治疗的效果。与其他遗传性心脏病相比,HCM 患病率最高,但预期寿命基本正常^[21]。考虑

到 HCM 病程的长期性, 在关注患者心脏相关症状的同时,也应该注意其认知功能的改变情况。但目前尚无针对 HCM 患者认知功能的相关研究。

本研究结果显示,认知功能障碍组 HCM 患者在各个认知领域均有不同程度受损,其中视空间与执行功能和延迟回忆方

表 2 两组患者认知功能比较

Table 2 Comparison of the cognitive function between two groups

Project	Cognitive impairment group	Normal cognitive function	t	P
	(n=37)	Group (n=161)		
Visuospatial and executive function	2.30± 1.18	4.11± 0.97	-7.293	<0.001
Naming	1.76± 1.12	2.68± 0.55	-5.498	<0.001
Delay memory	0.97± 1.01	3.12± 1.37	-7.349	<0.001
Attention	4.49± 1.45	5.76± 0.56	-6.688	<0.001
Language	1.35± 0.92	2.31± 0.82	-5.476	<0.001
Abstraction	0.65± 0.82	1.40± 0.70	-4.946	<0.001
Orientation	5.32± 0.75	5.81± 0.41	-4.566	<0.001
Total score of MoCA	17.65± 4.04	25.86± 2.57	-8.953	<0.001

Note: MoCA; Montreal Cognitive Assessment.

表 3 HCM 相关临床指标诊断 HCM 患者认知功能的敏感性与特异性分析及变量赋值

Table 3 Sensitivity and specificity of HCM-related clinical indexed in the diagnosis of cognitive function in HCM patients and variable assignment

Factors	AUC (95 %CI)	Sensitivity	Specificity	Cut-off value	P	Variable assignment
Age	0.729(0.662-0.790)	89.19	56.52	46.5	<0.001	≤ 46.5=0, >46.5=1
NYHA class	0.639(0.568-0.706)	75.68	51.88	1.5	0.002	≤ 1.5=0, >1.5=1
E/e'	0.608(0.535-0.679)	52.94	64.94	15.6	0.043	≤ 15.65=0, >15.65=1
LVOT-PG	0.660(0.587-0.727)	52.94	77.12	54.5	0.005	≤ 54.5=0, >54.5=1
Years of education	0.681(0.611-0.745)	72.97	55.90	9.0	<0.001	>9=0, ≤ 9=1

Note: AUC: area under curve; NYHA: New York Heart Association functional class; E/e': ratio of the early diastolic peak velocities of mitral inflow and mitral annulus; LVOT-PG: provoked left ventricular outflow tract pressure gradient.

表 4 HCM 患者认知功能障碍的危险因素的 Logistic 回归分析

Table 4 Logistic multivariate regression analysis of related factors of metabolic syndrome in HCM patients

Factors	Univariate analysis		Multivariate analysis	
	OR(95 %CI)	P	OR(95 %CI)	P
Age	10.725(3.630-31.691)	<0.001	14.435(4.476-46.550)	<0.001
NYHA class	3.354(1.488-7.557)	0.004	-	-
LVOT-PG	3.793(1.753-8.207)	0.001	3.844(1.551-9.524)	0.004
Years of education	3.423(1.554-7.537)	0.002	5.274(2.024-13.744)	0.001

Note: NYHA: New York Heart Association functional class; LVOT-PG: provoked left ventricular outflow tract pressure gradient.

面得分显著低于认知功能正常组。视空间功能障碍可导致患者空间工作记忆障碍、空间层次判断能力下降等^[22],影响其从事汽车驾驶、美术建筑等对空间层次能力和辨色能力要求较高的工作。执行功能障碍可导致患者合理规划、解决问题及注意判断等能力下降^[23],使其无法快速、准确的完成相对较为复杂的任务。延迟回忆障碍可导致患者新知识学习能力下降,严重者可影响日常生活,增加痴呆的发生风险^[24]。因此注重 HCM 患者早期认知功能评估十分重要,尤其是视空间与执行功能和延迟回忆的评估。

本研究发现,认知功能障碍组 HCM 患者左心室流出道压差较认知功能正常组升高,激发左心室流出道压差升高更为明显,差异具有统计学意义。多因素回归分析结果显示,激发左心室流出道压差是 HCM 患者发生认知功能障碍的独立危险因素。在运动负荷增加时, HCM 患者外周血管阻力明显变大,以

维持收缩压峰值和平均动脉压的基本正常。但左心室流出道压差升高可导致患者收缩压峰值和平均动脉压明显减低^[13]。此外,大约三分之一的 HCM 患者由于血管过度扩张而不能增加收缩压^[25],导致体动脉压下降,增加发生心力衰竭的风险^[26]。我们推测,高血管阻力和低体动脉压力可能会导致 HCM 患者心脑灌注不足,影响脑血流的自动调节功能,进而诱发脑慢性缺血缺氧性损伤。HCM 患者常伴有头晕、黑蒙、晕厥、劳力性气促等临床症状,反证了我们的推测。HCM 患者存在自主神经功能紊乱、心率变异性降低等改变,可影响到心脏的传导组织,进而发生恶性心律失常^[27]。而左心室流出道压差升高,能增加 HCM 快速心律失常的发生率,如室速和室颤^[27,28]。我们推测,心率变异性降低及恶性心律失常可能会增加 HCM 患者的血压变异性,进而导致脑血流自动调节功能紊乱和脑血管反应性的改变,增加了认知功能障碍发生的风险。

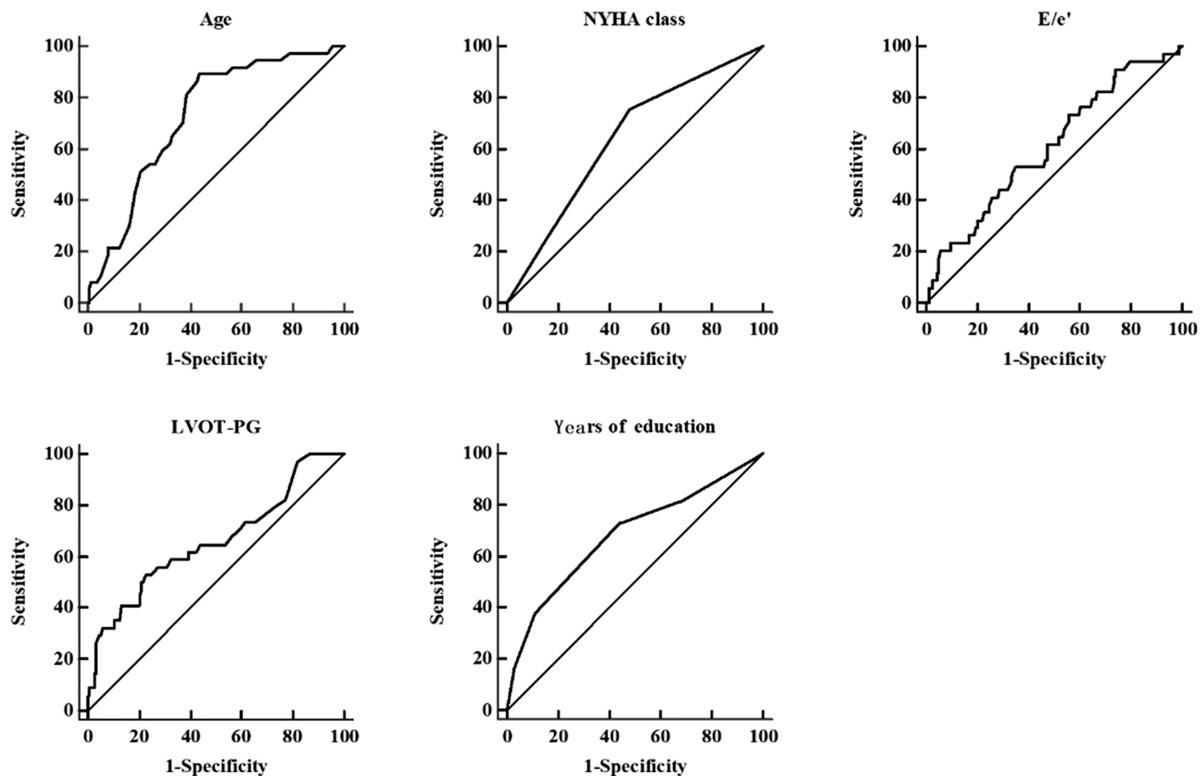


图 1 HCM 相关临床指标预测 HCM 患者认知功能的 ROC 曲线分析

Fig.1 ROC curve analysis of cognitive function in patients with HCM-related clinical indexes

Note: NYHA: New York Heart Association functional class; E/e': ratio of the early diastolic peak velocities of mitral inflow and mitral annulus; LVOT-PG: provoked left ventricular outflow tract pressure gradient.

本研究表明,年龄是 HCM 患者认知功能障碍的独立危险因素。一项关于年龄的纵向研究显示,随着年龄的增长,脑血管反应性减低,中年人减低较老年人明显,颞叶血管减低较枕叶明显;脑血管反应性减低与认知功能障碍相关,尤其影响处理速度和情景记忆^[29]。本研究纳入的 HCM 患者大部分为中年人,年龄可能影响其脑血管反应性,进而影响其执行功能和延迟回忆认知域。教育程度是认知功能障碍的重要保护因素之一。对 15 个前瞻性队列研究的 meta 分析发现,教育年限每增加一年,认知功能障碍的发生率降低 7%^[30]。教育可以增加认知储备,进而延缓认知功能障碍的发展^[31]。但本研究纳入的样本量较小,需要大样本进一步研究明确 HCM 认知功能障碍的危险因素。

综上,本研究表明激发左心室流出道压差可增加 HCM 患者认知功能障碍的发生风险。临床中应注意监测,预防 HCM 患者认知功能障碍的发生和发展。

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