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最小左房容积对非梗阻性肥厚型心肌病患者心血管事件的预测价值

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[摘　要]　**目的：**探索最小左房容积(left atrial minimal volume，LAV_{min})预测非梗阻性肥厚型心肌病(hypertrophic cardiomyopathy，HCM)患者发生心血管事件的应用价值，并对最小(LAV_{min})和最大左房容积(left atrial maximum volume，LAV_{max})两个参数的预测价值进行比较。**方法：**共纳入167例非梗阻性HCM患者，年龄为(64.6±13.4)岁，男女比例为120:47。将患者相关临床资料和超声心动图相关参数进行统计分析，并随访记录患者发生不良心血管事件(心力衰竭住院、卒中、死亡)。将发生心血管事件的人群纳入观察组，剩余为对照组。**结果：**患者跟踪随访(25.0±17.7)个月，有35例发生了心血管不良事件，纳入观察组；观察组LAV_{max}，LAV_{min}均较对照组增加，差异有统计学意义，均$P<0.001$；多因素分析发现调整相关年龄，糖尿病，高血压，心房颤动等参数后LAV_{min}，LAV_{max}与心血管发生事件独立相关；受试者工作特征(receiver operating characteristic，ROC)曲线分析发现对非梗阻性HCM患者，LAV_{min}比LAV_{max}预测价值更大(曲线下面积分别为0.85和0.82，$P=0.02$)。**结论：**LAV_{min}与非梗阻性HCM患者发生心血管事件独立相关，且其预测价值较LAV_{max}更好。

[关键词]　最小左房容积；预测；非梗阻性肥厚型心肌病；心血管事件

Diagnostic value of left atrial minimal volume on cardiovascular events in patients with non-obstructive hypertrophic cardiomyopathy

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Abstract　**Objective:** To investigate the prognostic role of left atrial minimal volume (LAV_{min}) in patients with non-obstructive hypertrophic cardiomyopathy (HCM) and to test if LAV_{min} is better than left atrial maximum volume (LAV_{max}) in predicting clinical outcome. **Methods:** A total of 167 consecutive patients with non-obstructive HCM were enrolled [age (64.6±13.4) years, male:female = 120:47]. Patients had cardiovascular events (heart failure

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hospitalization, stroke, death) were also investigated. Clinical parameters and conventional echocardiographic measurement were measured. The relationship between LAV_{min} and the clinical outcome was evaluated. **Results:** During a median follow-up of (25.0±17.7) months, the cardiovascular events occurred in 35 patients (21%). And the 35 patients were placed in the observation group. LAV_{max} and LAV_{min} were higher in the observation group than the control group (all P<0.001). By means of multi-variable analysis, we found that LAV_{min} and LAV_{max} were predictive of cardiovascular events after adjustment for age, diabetes, hypertension, atrial fibrillation, LV ejection fraction, and E/e' (P=0.001). By ROC analysis, we found that the model including indexed LAV_{min} was superior to the model including indexed LAV_{max} in predicting a worse outcome in patients with HCM (0.85 vs 0.82, P=0.02). **Conclusion:** LAV_{min} is independently associated with increased risk of HF, stroke, or mortality in patients with HCM and is superior to LAV_{max} in predicting clinical outcome in this population.

Keywords left atrial minimal volume; prognosis; non-obstructive hypertrophic cardiomyopathy; cardiovascular events

肥厚型心肌病(hypertrophic cardiomyopathy，HCM)是一种遗传性心肌病，以心肌肥大为主要特征[1-3]。临床中很多患者并无明显症状，还有一部分患者病情逐渐加重，最终出现临床表征[4-5]，其中心源性猝死和心力衰竭是HCM最严重的并发症。HCM往往伴随左室流出道梗阻，可引起心房颤动，甚至导致死亡[6-7]。非梗阻性HCM患者相对于梗阻性HCM其预后较好，而且心力衰竭发生率显著下降[8-9]。但是非梗阻性HCM患者由于心肌收缩和舒张功能障碍，其心房颤动发生风险较高，导致血栓形成，增加患者心血管死亡风险[10]。因此积极找寻预测非梗阻性HCM发生心血管发生事件的相关标志物对于延长患者的生存期具有至关重要的意义。

大量研究[11-13]已证实左房容积(left atrial volume，LAV)是评估心血管发生事件最有力的预测因子。当左心室舒张功能障碍时，左心房通过调整存储等再分配血液，使左心室有足够的血液充盈，保持正常的心输出量。左心室的容积大小可以反映左心室的舒张功能。在HCM有关的研究[14-18]中已经确定LAV与运动耐量，心房颤动的发生，不良预后相关。既往认为最大LAV容积(LAV_{max})受到左心室的舒张功能的影响，是预测心血管事件的标志物[19]。而最新研究证实最小LAV容积(LAV_{min})较LAV_{max}能更好反映左心室的舒张功能[20-21]。目前尚无关于LAV_{min}对非梗阻性HCM患者发生心血管事件的相关性研究。因此本研究拟探索对于非梗阻性HCM患者LAV_{min}指数预测心血管发生事件的价值，并将LAV_{min}和传统LAV_{max}进行比较，旨在为临床诊断提供理论依据。

1 对象与方法

1.1 对象

选取2012年1月至2016年1月恩施土家族苗族自治州中心医院内科心血管病中心门诊及病房被确诊为非梗阻性HCM的患者167例为研究对象，其中男120例，女47例。记录患者的年龄、性别、既往病史以及用药史等临床资料。本研究获得恩施土家族苗族自治州中心医院医学伦理委员会审核批准，患者均知情同意。

1.2 方法

1.2.1 诊断标准[1-2]

经过超声心动图检查，患者左心室和/或室间隔已增厚15 mm。并排除其他可能表现相似的疾病，如法布雷病，淀粉样变病等。

1.2.2 分组

对患者跟踪随访(25.0±17.7)个月，167例患者中，有35例患者发生心血管事件(8例发生死亡，9例发生心力衰竭而住院，18例发生卒中)，将发生心血管事件的35例患者设为观察组，未发生心血管事件的132例设为对照组。

1.2.3 仪器[22]

两组患者均采用探头频率为2.5~3.5 MHz的GE Vivid彩色多普勒显像仪进行检查，在检查中用二维超声双平面Simpson法对患者左心房内径和下径以及左右径进行测量，同时对非对称性室间隔、左心室后壁及左心室射血分数等进行测量。

1.2.4 观察指标

观察两组患者左心室舒张末期内径(left

ventricular end diastolic diameter，LVEDD)、收缩末期左室内径(left ventricular end systolic diameter，LVESD)、左心室射血分数(left ventricular ejection fraction，LVEF)、最大厚壁、减速时间(deceleration time，DT)、E/A值(左心室舒张早期最大血流与二尖瓣晚期流速峰值的比值)、E/e'值(二尖瓣瓣口血流流速曲线中舒张早期左室充盈速度与二尖瓣环舒张早期血流速度的比值)、左房容积指数(LAVI，包括最大值LAV_{max}和最小值LAV_{min})等指标。

1.3 统计学处理

采用STATA 14.0软件进行数据分析，计量资料采用均数±标准差($\bar{x}\pm s$)表示，行t检验，计数资料采用χ^2检验。对于获得的有统计学意义的单因素指标进行多元逻辑回归分析。使用受试者工作特征(receiver operating characteristic，ROC)曲线评估多元回归分析获得的参数的预测性能。P<0.05为差异有统计学意义。

2 结果

将纳入患者一般情况进行统计分析，见表1。本研究共纳入167例患者，年龄为(64.6±13.4)岁，女性47例(占28%)。对疾病组成进行分析发现：67例为高血压患者，42例为糖尿病患者，34例为心房颤动患者。50%患者临床上并无明显症状。

患者跟踪随访(25.0±17.7)个月，35例患者发生心血管事件，其中8例(5%)死亡，9例(5%)发生心力衰竭而住院，18例(11%)发生卒中。将发生心血管事件的35例患者设为观察组，未发生心血管事件的132例设为对照组。两组患者的临床和超声心动图相关参数的统计分析结果见表2。

临床资料结果显示：观察组较对照组年龄大，心房颤动发生率增加，差异有统计学意义(均P<0.001)；而性别、高血压比例、糖尿病比例差异无统计学意义(P>0.05)。超声心动图相关参数结果显示：观察组LAV_{max}，LAV_{min}，以及E/e'均较对照组增加，差异有统计学意义(均P<0.001)。其余超声相关参数差异无统计学意义(P>0.05)。

以年龄，心房颤动，E/e'，LAV_{max}，LAV_{min}作为自变量，以心血管发生事件作为因变量进行逻辑回归分析，见表3。单变量回归结果发现，年龄，心房颤动，E/e'，LAV_{max}，LAV_{min}均与心血管发生事件相关，均P<0.05，以这些为自变量构建多元逻辑回归模型。在多因素分析中发现，LAV_{max}，LAV_{min}均与心血管发生事件独立相关。

表1 纳入患者的一般情况

Table 1 Baseline characteristics of patients

变量	数值
年龄 / 岁	64.6 ± 13.4
女性 /[例 (%)]	47 (28)
高血压 /[例 (%)]	67 (40)
糖尿病 /[例 (%)]	42 (25)
心房颤动 /[例 (%)]	34 (20)
阵发性心房颤动 /[例 (%)]	9 (5)
持续性 / 永久性心房颤动 /[例 (%)]	25 (15)
症状 /[例 (%)]	
无症状	83 (50)
胸痛	29 (17)
心悸	8 (5)
头晕	3 (2)
晕厥	3 (2)
纽约心脏协会 (NYHA) 心功能分级	
I	119 (71)
II	39 (23)
III/IV	9 (5)
药物治疗 /[例 (%)]	
β 受体阻滞药	99 (59)
血管紧张素转换酶抑制药 (ACEI) 或血管紧张素受体阻滞药 (ARB)	53 (32)
钙通道阻滞药	48 (29)
利尿药	35 (21)
抗心律失常药物	7 (4)
抗血小板药物	35 (21)
抗凝药	31 (19)
他汀类药物	56 (34)

表2 临床与超声心动图相关参数与临床结果之间的单变量关系

Table 2 Univariate relations of clinical and echocardiographic parameters with clinical outcomes

临床相关因素	对照组(*n*=132)	观察组(*n*=35)	*P*
年龄/岁	63.7 ± 13.3	72.6 ± 12.1	<0.001
女性/[例(%)]	33 (25)	14 (40)	0.08
高血压/[例(%)]	50 (38)	17 (49)	0.25
糖尿病/[例(%)]	33 (25)	9 (26)	0.93
心房颤动/[例(%)]	18 (14)	16 (46)	<0.001
超声心动图相关参数			
LVEDD指数/($mm \cdot m^{-2}$)	26.4 ± 3.2	27.9 ± 3.4	0.58
LVESD指数/($mm \cdot m^{-2}$)	16.4 ± 2.6	16.5 ± 2.6	0.56
LVEF/%	63.5 ± 4.5	64.2 ± 5.6	0.61
LAV_{max}/($mL \cdot m^{-2}$)	38.2 ± 14.7	59.4 ± 23.2	<0.001
LAV_{min}/($mL \cdot m^{-2}$)	20.4 ± 11.3	43.5 ± 20.3	<0.001
最大厚壁/mm	20.1 ± 4.6	20.1 ± 3.5	0.98
E/($cm \cdot s^{-1}$)	64.5 ± 20.1	72.3 ± 20.7	0.08
A/($cm \cdot s^{-1}$)	132.3 ± 54.3	74.5 ± 22.4	0.65
E/A	0.98 ± 0.42	0.97 ± 0.51	0.99
DT/($ms \cdot s^{-1}$)	256.6 ± 70.43	247.4 ± 76.2	0.50
E/e’	13.5 ± 4.9	17.8 ± 7.5	<0.001

表3 单变量和多变量模型的风险比(95%CI)

Table 3 Hazard ratios (95% CIs) for composite outcome in univariate and multivariate Cox models

因素	单变量			多变量 I			多变量 II		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
年龄	1.06	1.01~1.13	0.02	1.04	0.99~1.11	0.14	1.04	0.98~1.11	0.24
心房颤动	3.06	1.13~8.30	0.03	1.21	0.39~3.76	0.75	0.87	0.25~3.05	0.82
E/e’	1.09	1.02~1.15	0.01	1.03	0.98~1.11	0.36	1.04	0.99~1.11	0.23
LAV_{max}	1.06	1.03~1.08	<0.001	1.05	1.03~1.17	0.001	—	—	—
LAV_{min}	1.06	1.04~1.09	<0.001	—	—	—	1.07	1.04~1.08	0.001

本研究分别构建了2个多元模型(I和II)。模型I纳入变量为年龄、心房颤动、LVEF、E/e’，LAV_{max}；模型II纳入变量为年龄、心房颤动、LVEF、二尖瓣晚期流速峰值/二尖瓣环运动速度、LAV_{min}(图1)。结果显示，模型I的曲线下面积(0.82，95%CI 0.73~0.90)小于模型II(0.85，95%CI 0.77~0.93)，差异有统计学意义(*P*=0.02)。

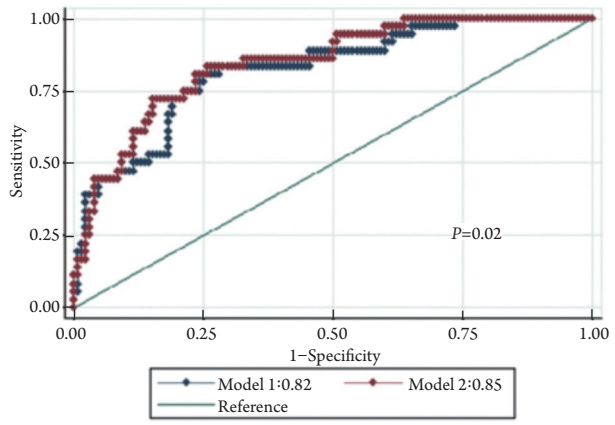

图1 不同模型的ROC曲线

Figure 1 ROC curves of the models

3 讨论

HCM在临床上表现多样，其中左室流出道梗阻与HCM的发病率和病死率独立相关[6-7]。非梗阻性HCM患者临床表现往往不易察觉，甚至有研究认为非梗阻性HCM是良性的病变过程，然而也有一些临床研究证实HCM中仍有相当比例患者发生心血管事件[8-10,23]。笔者在随访过程中发现有21%非梗阻性HCM患者发生卒中、心力衰竭而住院，甚至死亡等心血管不良事件，提示应重视对这类患者的不良心血管发生事件。因此早期发现和诊断非梗阻性HCM至关重要。本研究发现LAV_{max}和LAV_{min}均与非梗阻性HCM心血管发生事件独立相关，而且LAV_{min}预测非梗阻性HCM发生心血管事件的价值更大，值得临床推广应用。

HCM患者常伴随左心房肥大。一般认为左心房的重建与心肌舒张功能障碍、心律失常有关。而且左心室肥大、左室流出道梗阻、二尖瓣关闭不全等也可导致左心房扩大。大量研究[16-17]证实LAV反映了HCM患者的疾病严重程度，可以预测疾病不良预后。在左心室收缩时，左心房可作为存储容器，故左心房的尺寸大小和功能也受到左心室影响。LAV_{max}在左心室收缩末期测的左房容积最大值，反映了左心室的舒张能力，可作为发生心血管疾病的潜在标志物，预测心血管事件的发生。但是LAV_{max}受到左心室收缩功能的影响[19,24]。LAV_{min}在左心室舒张末期测得的左房容积最小值，由于此时左心室处于舒张末期，故理论上LAV_{min}更能反映心室的左舒张能力[20,25]。当发生左心室舒张功能障碍时，LAV_{min}和LAV_{max}均升高，但LAV_{min}增加更显著[20]。此外大量研究[21,26]证实LAV_{min}与临床不良事件相关；LAV_{min}较LAV_{max}对预测老年人第1次发生心房颤动或心房扑动价值更大，本研究结果与此相符。本研究发现对于非梗阻性HCM患者，LAV_{min}对于心血管不良事件预测价值较LAV_{max}大。

本研究仍存在一些不足：1)纳入的样本数量有限，可能造成一定偏倚；2)为单中心研究，纳入的样本可能代表性不足。

综上，本研究证实LAV_{min}能预测非梗阻性HCM患者发生不良心血管事件的风险，而且LAV_{min}较LAV_{max}预测价值更大，更值得临床推广，但仍需要更大样本的研究验证本结论。

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