

• 临床研究 •

心房颤动伴中度及以上心房功能性二尖瓣反流患者的临床特征

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[摘要] 目的: 分析心房颤动(atrial fibrillation, AF)伴中度及以上心房功能性二尖瓣反流(atrial functional mitral regurgitation, AFMR)患者的临床特征和相关因素。方法: 本研究为单中心横断面研究。连续纳入2023年7月—2024年3月入住南京医科大学附属江宁医院心血管内科的AF伴AFMR患者共313例, 根据二尖瓣反流程度分为中度以下AFMR组(A组, 249例)与中度及以上AFMR组(B组, 64例)。比较基线资料, 采用Logistic回归分析AF伴中度及以上AFMR的相关因素。结果: 两组间年龄、CHA2DS2-VASc评分、房颤类型、肾功能不全病史、射血分数保留的心力衰竭(heart failure with preserved ejection fraction, HFpEF)病史、氨基末端脑钠肽前体(N-terminal pro-brain natriuretic peptide, NT-proBNP)、三尖瓣反流程度、左房内径、左室舒张末内径、左室射血分数差异有统计学意义($P < 0.05$)。多因素回归分析显示, 左房内径($OR=1.067$, 95%CI: 1.002~1.137, $P < 0.05$)、左室舒张末内径($OR=1.153$, 95%CI: 1.052~1.264, $P < 0.05$)、三尖瓣轻-中度反流($OR=6.571$, 95%CI: 1.362~31.705, $P < 0.05$)、三尖瓣中度反流($OR=10.795$, 95%CI: 3.816~30.543, $P < 0.05$)、三尖瓣中-重度反流($OR=19.525$, 95%CI: 4.593~82.999, $P < 0.05$)、三尖瓣重度反流($OR=20.701$, 95%CI: 5.799~73.896, $P < 0.05$)是AF伴中度及以上AFMR的独立危险因素。结论: 与AF伴中度以下AFMR患者相比, AF伴中度及以上AFMR患者具有不同的临床特征, 通常有更多的临床伴发疾病, 左房内径增大、左室舒张末内径增大和三尖瓣轻度以上反流是AF伴中度及以上AFMR的独立危险因素。

[关键词] 心房颤动; 心房功能性二尖瓣反流; 三尖瓣反流

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Clinical characteristics of patients with atrial fibrillation and moderate to severe atrial functional mitral regurgitation

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[Abstract] **Objective:** To investigate the clinical characteristics and identify the associated factors in patients with atrial fibrillation (AF) and moderate to severe atrial functional mitral regurgitation (AFMR). **Methods:** This was a single-center and cross-sectional study, which recruited a total of 313 patients with AF and AFMR hospitalized in the cardiovascular department of the Affiliated Jiangning Hospital of Nanjing Medical University from July 2023 to March 2024. Patients were categorized into two groups based on the severity of mitral regurgitation: the less than moderate AFMR group (Group A, $n=249$) and the moderate to severe AFMR group (Group B, $n=64$). Baseline data were compared, and correlation analysis and logistic regression were employed to determine the factors associated with moderate to severe AFMR in AF patients. **Results:** Significant differences ($P < 0.05$) were observed between the groups in age, CHA2DS2-VASc score, type of atrial fibrillation, history of renal insufficiency, heart failure with preserved ejection fraction (HFpEF), N-terminal pro-brain natriuretic peptide (NT-proBNP), tricuspid regurgitation severity, left atrial diameter, left ventricular end diastolic diameter, and left ventricular ejection fraction. Multivariate logistic regression analysis revealed that left atrial diameter ($OR=1.067$, 95% CI: 1.002–1.137, $P < 0.05$), left ventricular end diastolic diameter ($OR=1.153$, 95% CI: 1.052–1.264, $P < 0.05$), mild-to-moderate tricuspid regurgitation ($OR=6.571$, 95% CI: 1.362–31.705, $P < 0.05$), moderate tricuspid regurgitation ($OR=10.795$, 95% CI: 3.816–30.543, $P < 0.05$), moderate-to-severe tricuspid regurgitation ($OR=19.525$, 95% CI: 4.593–82.999, $P < 0.05$), and

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severe tricuspid regurgitation (OR=20.701, 95% CI: 5.799–73.896, $P < 0.05$) were independent risk factors for moderate to severe AFMR in AF patients. **Conclusion:** Compared with AF patients with AFMR less than moderate severity, those with moderate to severe AFMR show the discrepancy in clinical characteristics, and they tend to exhibit a more complex clinical comorbidities. Left atrial diameter enlargement, left ventricular end diastolic diameter enlargement, and the presence of more than mild severity of tricuspid regurgitation are independent predictors of moderate to severe AFMR in AF patients.

[Key words] atrial fibrillation; atrial functional mitral regurgitation; tricuspid regurgitation

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心房颤动(atrial fibrillation, AF)是最常见的心律失常之一^[1]。AF可造成胸闷、乏力、心悸、认知功能下降等症状,更可引起卒中、心力衰竭以及二尖瓣反流等并发症^[2]。二尖瓣反流与AF间有复杂的相互作用,由于二尖瓣反流造成左心房前负荷增加,可引起左心房扩张,进而导致或加重AF;而AF也可能通过二尖瓣环扩张、二尖瓣瓣环鞍形平坦化等途径导致或加重二尖瓣反流,即心房功能性二尖瓣反流(atrial functional mitral regurgitation, AFMR)^[3]。AF伴AFMR的病理生理机制目前尚未完全明确,但二者同时存在时可显著增加患者的病死率和心衰住院率^[4]。近年来,AF伴AFMR逐渐引起重视,但多聚焦于该类疾病的治疗及预后,鲜有关于临床特征及相关因素的报道;且既往研究常将轻度AFMR与中度及以上AFMR患者混合分析,忽视了轻度二尖瓣反流较高的人群发病率等混杂因素对研究结果的影响^[5]。本研究旨在通过比较AF伴中度及以上AFMR与中度以下AFMR患者的临床特征,探讨独立危险因素,为临床诊疗提供指导。

1 对象和方法

1.1 对象

连续纳入2023年7月—2024年3月于南京市江宁医院心血管内科住院的AF合并AFMR的患者共313例,其中轻度AFMR 219例(70.0%),轻-中度AFMR 30例(9.6%),中度AFMR 52例(16.6%),中-重度AFMR 8例(2.6%),重度AFMR 4例(1.3%),根据二尖瓣反流程度分为中度以下AFMR组(A组, $n=249$)与中度及以上AFMR组(B组, $n=64$)。AF的诊断标准参考2019年美国心脏协会/美国心脏病学会/心律协会的心房颤动管理指南定义^[6]。本研究经南京医科大学附属江宁医院医学伦理委员会批准(批准文号:20230102),符合赫尔辛基宣言。

AFMR的诊断标准:AFMR目前尚无统一诊断

标准,根据近年相关研究及发病机制,本研究中AFMR的诊断标准为:①二尖瓣瓣叶结构正常,无二尖瓣器质性病变;②左心房扩大,定义为左心房内径(left atrial diameter, LAD) >38 mm和/或左心房容积指数 >34 mL/m²;合并心房颤动和/或左室舒张功能不全;③左心室舒张末内径(left ventricular end diastolic diameter, LVEDd)无明显增大,即男性LVEDd ≤ 60 mm,女性LVEDd ≤ 55 mm;④左室射血分数(left ventricular ejection fraction, LVEF) $\geq 50\%$,且无节段性室壁运动异常^[2,7-9]。

入选标准:①心房颤动患者年龄 ≥ 18 岁;②具有轻度及以上的二尖瓣反流,且符合AFMR诊断标准。排除标准:①可逆因素(甲状腺功能异常、脓毒血症、1个月内的外科手术等)造成的房颤;②心脏外科术后、先天性心脏病、肥厚型心肌病、限制性心肌病、缩窄性心包炎;③具有风湿性心脏病、任何程度的二尖瓣及主动脉瓣狭窄,或中度以上的主动脉瓣反流。

1.2 方法

记录入组患者人口学资料与临床资料,包括性别、年龄、身高、体重、体重指数(body mass index, BMI)、房颤症状、房颤类型、房颤病程、CHA2DS2-VASc评分、高血压史、糖尿病史、缺血性卒中史、外周血管疾病史、血肌酐水平、氨基末端脑钠肽前体(N-terminal pro-brain natriuretic peptide, NT-proBNP)水平、用药情况及超声心动图相关结果等,其中二尖瓣、三尖瓣反流程度依据《中国成人心脏瓣膜病超声心动图规范化检查专家共识》评估^[10],CHA2DS2-VASc评分、欧洲心律学会(European Heart Rhythm Association, EHRA)评分、高血压史、糖尿病史、缺血性卒中史、外周血管疾病史的评分及诊断标准参照《心房颤动诊断和治疗中国指南》^[11]。Cockcroft-Gault公式估计肾小球滤过率(estimated glomerular filtration rate, eGFR)低于60 mL/(min \cdot 1.73 m²)时定

义为肾功能不全^[12];HFpEF依据《射血分数保留的心衰诊断与治疗中国专家共识2023》进行诊断^[13]。

1.3 统计学方法

应用SPSS26.0统计软件分析,计量资料通过Shapiro-Wilktest检验确定是否符合正态分布,符合正态分布的计量资料以均数 \pm 标准差($\bar{x} \pm s$)来表示,组间比较采用 t 检验;不符合正态分布的计量资料以中位数(四分位数)[$M(P_{25}, P_{75})$]表示,组间比较采用秩和检验。计数资料以频数及百分比表示,组间比较采用卡方检验。分别采用单因素Logistic回归分析和多因素Logistic回归分析识别AF伴中度及以上AFMR的危险因素。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组基线资料比较

如表1所示,两组患者基线资料中,年龄、CHA2DS2-VASc评分、房颤类型、HFpEF史、肾功能不全史、抗凝药物、血肌酐、eGFR、NT-proBNP、三尖瓣反流程度、LAD、LVEDd及LVEF差异有统计学意义($P < 0.05$);其余基线资料比较,差异均无统计学意义($P > 0.05$)。

2.2 AF伴中度及以上AFMR相关因素分析

单因素Logistic模型分析提示年龄、CHA2DS2-VASc评分、肾功能不全、持续性AF、新型口服抗凝药(novel oral anticoagulant, NOAC)、血肌酐、eGFR、NT-proBNP、HFpEF、三尖瓣轻度以上的反流、LAD、LVEDd及LVEF与AF患者伴中度及以上AFMR相关(表2),以上述指标及房颤病程、节律控制药物、心率控制药物、导管消融作为自变量,AF伴中度及以上AFMR作为因变量进行多因素Logistic回归分析,结果示LAD(OR=1.067, 95%CI: 1.002~1.137, $P < 0.05$)、LVEDd(OR=1.153, 95%CI: 1.052~1.264, $P < 0.05$)、三尖瓣轻度以上反流[包括三尖瓣轻-中度反流(OR=6.571, 95%CI: 1.362~31.705)、三尖瓣中度反流(OR=10.795, 95%CI: 3.816~30.543)、三尖瓣中-重度反流(OR=19.525, 95%CI: 4.593~82.999)、三尖瓣重度反流(OR=20.701, 95%CI: 5.799~73.896)]是AF伴中度及以上AFMR发生的独立危险因素($P < 0.05$, 表3)。

3 讨论

继发性二尖瓣反流,即功能性二尖瓣反流(functional mitral regurgitation, FMR),最初被定义为

由扩张型心肌病或缺血性心脏病所致的乳头肌功能失调、左心室收缩功能障碍和重塑引起的二尖瓣小叶牵张所致^[14]。2011年Gertz等^[15]发现并报道了部分AF患者具有大致正常的左心室大小及收缩功能,但合并显著的FMR,且通过导管消融多数患者的二尖瓣反流得到明显改善,进而提出AFMR的概念。AF伴AFMR的机制尚不明确,AF引起的左心房增大、二尖瓣环扩张和二尖瓣反流的顺序关系仍有争议,目前认为AF患者发生AFMR的可能机制包括二尖瓣环扩大造成的瓣叶栓系、二尖瓣叶重塑不足及二尖瓣环动力学障碍、左室舒张功能不全及左房压升高等^[3]。本研究发现左心房和左心室扩大是AF伴AFMR的独立危险因素,而左心房、左心室的扩张可引起二尖瓣环的扩张,使二尖瓣附着点向外移位,进而使得二尖瓣闭合面积下降;此外,左心室扩大可能造成乳头肌与二尖瓣环间的距离增加,因腱索牵拉导致相应二尖瓣叶在心室收缩期无法充分闭合(即二尖瓣栓系),造成更为严重的二尖瓣反流。

与二尖瓣反流相比,三尖瓣反流通常被认为与AF的关系更紧密,也更常见,但受到的关注却更少^[16]。随着AFMR受到日益重视,心房功能性三尖瓣反流(atrial functional tricuspid regurgitation, AFTR)与AF的关系逐渐被揭示。类似AFMR,AFTR的发生主要也是由于三尖瓣环的扩张和瓣叶的栓系造成,主要发生在三尖瓣后缘^[17]。目前针对AFTR尚无标准治疗方案,利尿剂等内科治疗无法改善AFTR患者的预后,而外科手术及介入手术因较低的获益-风险比,很少单独行三尖瓣手术治疗^[18]。但既往研究发现,仅针对左心的操作却可能影响三尖瓣反流情况,如二尖瓣反流外科手术、房颤导管消融后三尖瓣反流可显著改善,而左心耳封堵却可在短期内加重三尖瓣反流程度,提示三尖瓣反流可能受到左房收缩功能、左房压力、左房僵硬度等因素的影响^[19]。本研究中,轻度以上的三尖瓣反流是AF伴中度以上AFMR的独立危险因素,且三尖瓣反流越严重,与AF伴中度以上AFMR的相关性越高。AF是心房整体性疾病,可同时影响左右心房甚至心室的结构、功能,进而造成AFMR、AFTR同时发生。需强调的是,虽未列入排除标准,但本研究患者队列中并无三尖瓣叶毁损、右心室乳头肌病变等三尖瓣装置器质性病变造成的三尖瓣反流,所有三尖瓣反流患者均为功能性三尖瓣反流。

由于AF伴AFMR独特的发病机制及其对临床心血管事件的显著影响,近年来已逐渐引起重视,

表1 两组患者基线资料比较

Table 1 Comparison of baseline data between the two groups

Variable	Group A (n=249)	Group B (n=64)	$t/\chi^2/z$	P
Female[n(%)]	116(46.59)	33(51.56)	0.505	0.477
Age[years, $M(P_{25}, P_{75})$]	75(69, 81)	79.5(73, 85)	-3.353	0.001
BMI(kg/m ² , $\bar{x} \pm s$)	25.41 \pm 3.91	24.46 \pm 4.18	1.715	0.087
EHRA score[n(%)]			2.734	0.434
Grade I	16(6.43)	4(6.25)		
Grade II	61(24.50)	16(25.00)		
Grade III	102(40.96)	20(31.25)		
Grade IV	70(28.11)	24(37.50)		
CHA2DS2-VASc score[$M(P_{25}, P_{75})$]	4(3, 5)	5(4, 6)	-2.695	0.007
Duration of atrial fibrillation[years, $M(P_{25}, P_{75})$]	2(1, 6)	2(1, 6)	-0.994	0.320
Persistent atrial fibrillation[n(%)]	159(63.86)	53(82.81)	8.372	0.004
HFpEF[n(%)]	127(51.00)	50(78.13)	15.241	<0.001
Hypertension[n(%)]	185(74.30)	44(68.75)	0.798	0.372
Diabetes[n(%)]	48(19.28)	17(26.56)	1.642	0.200
Ischemic stroke[n(%)]	58(23.29)	16(25.00)	0.082	0.774
Peripheral vascular disease[n(%)]	90(36.14)	28(43.75)	1.254	0.263
Renal insufficiency[n(%)]	81(32.53)	34(53.13)	9.291	0.002
Treatment of atrial fibrillation[n(%)]			4.059	0.255
None	83(33.33)	24(37.50)		
Rhythm control drug	7(2.81)	0(0)		
Catheter ablation	26(10.44)	3(4.69)		
Heart rate control medication	133(53.41)	37(57.81)		
Anticoagulants[n(%)]			9.455	0.009
None	27(10.84)	17(26.56)		
NOAC	219(87.95)	47(73.44)		
Warfarin	3(1.20)	0(0)		
RASSi[n(%)]	127(51.00)	29(45.31)	0.660	0.417
β -receptor blocker[n(%)]	141(56.63)	34(53.13)	0.253	0.615
SGLT2i[n(%)]	75(30.12)	22(34.38)	0.431	0.512
Spironolactone[n(%)]	37(14.86)	11(17.19)	0.213	0.645
Statin[n(%)]	204(81.93)	52(81.25)	0.016	0.900
Serum creatinine[μ mol/L, $M(P_{25}, P_{75})$]	72.5(61.65, 90.65)	85.35(65.63, 120.03)	-2.586	0.010
eGFR[mL/(min \cdot 1.73 m ²), $M(P_{25}, P_{75})$]	68.15(50.46, 86.13)	50.90(33.40, 77.35)	-3.596	<0.001
NT-proBNP[pg/mL, $M(P_{25}, P_{75})$]	805.00(364.50, 1514.00)	1 596.00(821.00, 3 208.75)	-4.979	<0.001
Tricuspid regurgitation degree[n(%)]			83.264	<0.001
None	2(0.80)	2(3.13)		
Mild	159(63.86)	4(6.25)		
Light-to-moderate	14(5.62)	4(6.25)		
Moderate	47(18.88)	29(45.31)		
Moderate-to-severe	13(5.22)	8(12.50)		
Serious	14(5.62)	17(26.56)		
LAD[mm, $M(P_{25}, P_{75})$]	43(38, 47)	49(44, 52)	-6.406	<0.001
LVEDd(mm, $\bar{x} \pm s$)	46.22 \pm 4.36	49.45 \pm 5.60	-4.965	<0.001
LVEF[%, $M(P_{25}, P_{75})$]	65(60, 68)	63(57, 66)	-2.552	0.011

BMI: body mass index; HFpEF: heart failure with preserved ejection fraction; NOAC: novel oral anticoagulant; RASSi: inhibitor of the renin-angiotensin system; SGLT2i: sodium-glucose co-transporter 2 inhibitor; eGFR: estimated glomerular filtration rate; LAD: left atrial diameter; LVEDd: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction. Rhythm control drugs: including Class Ic and Class III antiarrhythmic drugs; heart rate control medication: including β -receptor blocker, digoxin, and non-dihydropyridine calcium antagonists.

表2 单因素Logistic回归分析
Table 2 Univariate logistic regression analysis

Variable	OR	95%CI	P
Female	1.221	0.704–2.115	0.477
Age	1.047	1.014–1.081	0.005
BMI	0.940	0.875–1.009	0.088
EHRA score grade II	1.049	0.308–3.576	0.939
EHRA score grade III	0.784	0.237–2.593	0.691
EHRA score grade IV	1.371	0.417–4.507	0.603
CHA2DS2-VASc score	1.214	1.047–1.406	0.010
Hypertension	0.761	0.418–1.387	0.373
Diabetes	1.515	0.800–2.866	0.202
Ischemic stroke	1.098	0.580–2.077	0.774
Vascular disease	1.374	0.787–2.399	0.264
Renal insufficiency	2.351	1.345–4.107	0.003
Course of atrial fibrillation	1.013	0.954–1.077	0.665
Persistent atrial fibrillation	2.727	1.356–5.486	0.005
Rhythm control drug	0	0	0.999
Catheter ablation	0.399	0.111–1.433	0.159
Heart rate control medication	0.962	0.537–1.722	0.897
NOAC	0.341	0.172–0.675	0.002
RASSi	0.796	0.459–1.381	0.417
β-receptor blocker	0.868	0.500–1.506	0.615
SGLT2i	1.215	0.679–2.176	0.512
MRA	1.189	0.569–2.486	0.645
Statin	0.956	0.472–1.936	0.900
Serum creatinine	1.011	1.004–1.019	0.003
eGFR	0.983	0.972–0.994	0.002
NT-proBNP	1.000	1.000–1.000	<0.001
HFpEF	3.431	1.804–6.524	<0.001
Mild-to-moderate tricuspid regurgitation	7.667	1.933–30.413	0.004
Moderate tricuspid regurgitation	16.557	6.486–42.265	<0.001
Moderate-to-severe tricuspid regurgitation	16.513	4.974–54.82	<0.001
Severe tricuspid regurgitation	32.583	11.075–95.861	<0.001
LAD	1.151	1.096–1.208	<0.001
LVEDd	1.153	1.085–1.226	<0.001
LVEF	0.936	0.893–0.983	0.007

EHRA score was subject to EHRA score grade I as the reference; tricuspid regurgitation was subject to no tricuspid regurgitation+mild tricuspid regurgitation as the reference.

但既往研究多集中于该类患者的治疗及预后情况，对其临床特征，尤其对不同程度 AFMR 进行比较的研究鲜有报道，且多数研究将中度以下二尖瓣反流与更严重的二尖瓣反流患者混杂分析^[20–22]，而大规模流行病学研究已指出，对于 30 岁以上的人群，轻度二尖瓣反流的发病率可高达 67% 以上^[5]。本研究发现，与 A 组患者相比，B 组患者年龄更大，CHA2DS2-VASc 评分更高，更多患者伴有肾功能不全

及 HFpEF，NT-proBNP 水平也更高，而既往研究发现，年龄、CHA2DS2-VASc 评分、HFpEF、NT-proBNP 等因素与该类患者预后明确相关性^[23]，提示这两类患者具有较大的临床特征及预后差异，故建议在后续 AF 伴 AFMR 的临床特征及预后等相关研究中，将 AF 伴中度及以上 AFMR 患者与中度以下 AFMR 患者分别分析，否则结果可能产生较大偏差。此外，在临床中发现 AF 伴 AFMR 患者具有明显三尖瓣

表3 多因素Logistic回归分析
Table 3 Multivariate logistic regression analysis

Variable	OR	95%CI	P
Age	0.975	0.921-1.033	0.397
CHA2DS2-VASc score	1.111	0.888-1.389	0.358
Renal insufficiency	2.250	0.908-5.575	0.080
Persistent atrial fibrillation	0.835	0.303-2.299	0.726
NOAC	0.386	0.144-1.036	0.059
Serum creatinine	0.995	0.980-1.010	0.485
eGFR	0.991	0.962-1.020	0.520
NT-proBNP	1.000	1.000-1.000	0.522
HFpEF	1.038	0.395-2.731	0.939
Course of atrial fibrillation	0.949	0.879-1.024	0.178
Rhythm control drug	0.912	0.329-2.529	0.859
Catheter ablation	0.000	0.000-0.000	0.999
Heart rate control medication	1.656	0.267-10.259	0.588
Mild-to-moderate tricuspid regurgitation	6.571	1.362-31.705	0.019
Moderate tricuspid regurgitation	10.795	3.816-30.543	<0.001
Moderate-to-severe tricuspid regurgitation	19.525	4.593-82.999	<0.001
Severe tricuspid regurgitation	20.701	5.799-73.896	<0.001
LAD	1.067	1.002-1.137	0.044
LVEDd	1.153	1.052-1.264	0.002
LVEF	0.952	0.892-1.016	0.140

Tricuspid regurgitation was subject to no tricuspid regurgitation+mild tricuspid regurgitation as the reference.

反流、较大的左心房与左心室时应积极治疗,防止AFMR进一步恶化。本研究为单中心观察性研究,研究对象为住院患者,病情较严重,可能具有选择偏倚;入组患者中仅4例患者无三尖瓣反流,故Logistic回归分析中将三尖瓣无反流患者与三尖瓣轻度反流患者合并作为参照。后期课题组将继续增加样本量,并追踪随访数据,以求获得更加客观、全面的研究结果。

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