· 临床研究 ·

DR-FLASH 评分联合左房心外膜脂肪对非瓣膜性心房颤动左房低电压的预测价值

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【摘 要】 目的 探讨 DR-FLASH 评分和左房心外膜脂肪(LA-EAT)体积的相关性及二者联合预测非瓣膜性心房颤动(简称房颤)左房低电压区域(LVZ)的价值。**方法** 连续纳入 2019 年 9 月至 2021 年 4 月徐州医科大学附属医院心血管内科首次接受导管射频消融治疗的非瓣膜性房颤患者 246 例，所有患者均接受肺静脉计算机断层扫描血管造影(CTA)，并测量 LA-EAT 体积。根据患者入院情况计算 DR-FLASH 评分。术前进行肺静脉 CTA 扫描，计算测量 LA-EAT 体积。在术中窦性心律下，进行左房高密度电压标测，根据有无低电压(双极电压<0.5 mV)将患者分为 LVZ 组和无 LVZ 组。采用 SPSS 24.0 软件进行数据分析。根据数据类型，组间比较分别采用 t 检验、U 检验、χ^2 检验及方差分析。采用 Spearman 相关性分析确定 DR-FLASH 评分与 LA-EAT 体积之间的相关性。采用受试者工作特征(ROC)曲线分析 DR-FLASH 评分、LA-EAT 体积及其联合预测 LVZ 发生的价值。**结果** 最终纳入患者 246 例，平均年龄(60.8±10.6)岁，其中 56 例(22.8%)患者出现至少 1 个 LVZ。相关性分析显示 DR-FLASH 评分与 LA-EAT 体积呈正相关(r=0.439；P<0.001)。采用多因素分析显示 DR-FLASH 评分(OR=1.824，95%CI 1.390～2.394；P<0.001)和 LA-EAT 体积(OR=1.048，95%CI1.013～1.085；P=0.007)是左房 LVZ 的独立危险因素。结合 ROC 曲线，LA-EAT 体积、DR-FLASH 评分、LA-EAT 与 DR-FLASH 评分的 ROC 曲线下面积分别为 0.712、0.750、0.796。**结论** DR-FLASH 评分与 LA-EAT 体积呈正相关，DR-FLASH 评分和 LA-EAT 体积均为非瓣膜性房颤左房 LVZ 的独立预测因子。二者联合可提高对非瓣膜性房颤左房 LVZ 的发生预测价值。

【关键词】 心血管疾病；心房颤动；心外膜脂肪组织；心房纤维化；双极电压标测；DR-FLASH 评分

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Predictive value of DR-FLASH score combined epicardial adipose tissue surrounding left atrium for left atrial low-voltage in patients with non-valvular atrial fibrillation

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【Abstract】 Objective To investigate the correlation between DR-FLASH score and epicardial adipose tissue (EAT) volume around the left atrium (LA), and explore the predictive value of their combination for left atrial low voltage zone (LVZ) in patients with non-valvular atrial fibrillation (NVAF). **Methods** A total of 268 NVAF patients who received radiofrequency catheter ablation for first time in Department of Cardiovascular Diseases, Affiliated Hospital of Xuzhou Medical University from September 2019 to April 2121 were consecutively recruited in this single-center retrospective clinical observation study. All patients underwent CTA scanning of pulmonary vein preoperatively, and then the volume of LA-EAT was measured. DR-FLASH score were calculated after admission. During the operation, the high-density voltage mapping of the LA was performed under sinus rhythm, and the patients were divided into LVZ group and non-LVZ group according to LVZ existence (bipolar voltage <0.5 mV as low voltage area). SPSS statistics 24.0 was used for statistical analysis. Intergroup comparison was performed using student's t test, U test or Chi-square test depending on data type. Spearman correlation analysis was employed to determine the correlation between DR-FLASH score and LA-EAT volume. Receiver operating characteristic (ROC) curve was plotted to analyze the value of DR-FLASH score, LA-EAT volume and their combination to

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predict LVZ occurrence. **Results** In the subjected 246 patients, their average age was (60.8±10.6) years, and at least one LVZ was found in 56 patients (22.8%). The correlation analysis showed that the DR-FLASH score was positively correlated with LA-EAT volume (r=0.439; P<0.001). Multivariate analysis revealed that DR-FLASH score (OR=1.824, 95%CI 1.390-2.394; P<0.001) and LA-EAT (OR=1.048, 95%CI 1.013-1.085; P=0.007) were independent risk factors for LVZ after radiofrequency catheter ablation. The area under the ROC curve was 0.712, 0.750 and 0.796, respectively for LA-EAT volume, DR-FLASH score, and their combination. **Conclusion** For NVAF patients, their DR-FLASH score is positively correlated with LA-EAT volume. The two indicators are independent predictors of left atrial LVZ in them. Their combination can improve the predictive value of left atrial LVZ in NVAF patients with non-valvular atrial fibrillation.

【Key words】 cardiovascular diseases; atrial fibrillation; epicardial adipose tissue; atrial fibrosis; bipolar voltage mapping; DR-FLASH score

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心房颤动(简称房颤)是最常见的具有临床意义的心律失常[1],以心房纤维化为特点的心房结构重构在房颤的发生和维持中起重要作用[2]。临床上评估心房心肌纤维化的主要方式有心内膜活检、心腔内电压标测低电压区、延迟钆增强心脏磁共振(late gadolinium enhancement cardiac magnetic resonance, LGE-CMR)等,但其都各有不足之处。寻找能够预测患者心房纤维化的无创指标对个体化消融有着重要的临床意义。DR-FLASH评分被认为能够有效评估心房纤维化程度,且队列组中也发现高DR-FLASH评分与房颤复发相关[3],但利用临床评分预测心房纤维化的研究尚不充分。最近研究表明[4],心外膜脂肪组织(epicardial adipose tissue, EAT)也与房颤发生和复发有关。本研究拟探讨DR-FLASH评分联合左房心外膜脂肪(left atrium epicardial adipose tissue, LA-EAT)体积是否能有效预测心房心肌纤维化的存在,报道如下。

1 对象与方法

1.1 研究对象

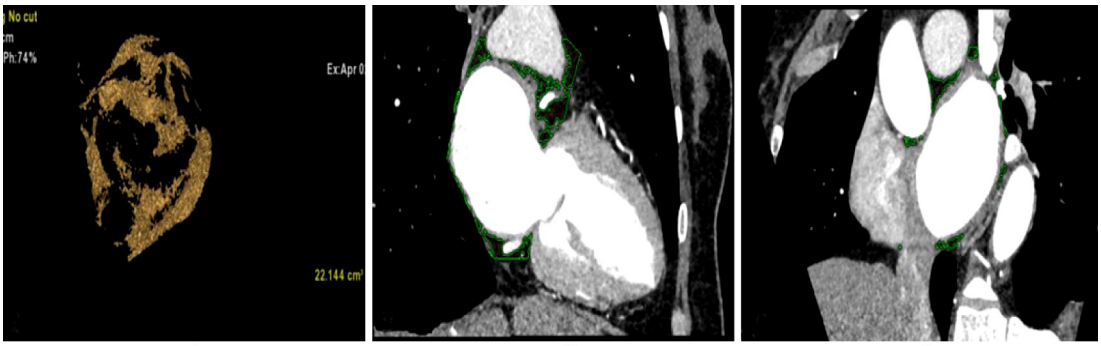
连续纳入2019年9月至2021年4月于徐州医科大学附属医院心血管内科行首次射频消融手术的非瓣膜病房颤患者246例,其中阵发性房颤143例,持续性房颤103例。所有患者均经过心电图和(或)动态心电图明确诊断房颤。阵发性房颤定义为房颤持续时间≤7 d,能自行终止;持续性房颤定义为持续7 d以上或需要电复律或药物转复来终止[5]。除胺碘酮外,所有Ⅰ类或Ⅲ类抗心律失常药物在房颤消融前至少停用5个半衰期。本研究已通过徐州医科大学附属医院伦理委员会审查(伦理号XYFY2021-KL223-01),所有患者均签署知情同意书。

纳入标准:(1)症状性房颤;(2)抗心律失常药物治疗无效或不能耐受;(3)权衡手术风险及疗效后主动选择射频消融。排除标准:(1)既往行房颤导管消融术和(或)其他心脏手术;(2)甲状腺功能亢进;(3)风湿性及其他心脏瓣膜病;(4)活动性结缔组织病;(5)因造影剂过敏等原因无法接受左房肺静脉血管成像(computer tomography angiography, CTA)检查;(6)术前接受左房肺静脉CTA和经胸超声心动图检查发现左房血栓和血流动力学显著结构异常。

1.2 方法

1.2.1 CTA扫描及图像后处理测量 影像学资料均采用螺旋CT机(SOMATOM Definition, SIEMENS Germany)获得。将对比剂(60~80 ml的碘海醇及50 ml的生理盐水)于肘静脉推注,流速5 ml/s。在6 s延迟后,运用了对比剂追踪技术至升主动脉根部水平触发一次5~12 s的增强扫描。触发阈值:90~100 Hu;扫描参数:管内电流280~350 mA,管内电压120 kV;扫描区域:气管隆突下1.0 cm至心脏下缘1.5 cm。所有图像采用回顾性心电门控重建,层厚0.5 mm,重叠0.3 mm,利用(Advandvage Workstation3.2, GE, USA)工作站进行图像后处理。从肺动脉分叉到心尖,采用人工逐层勾画心包边界确定感兴趣区,将脂肪组织CT值阈值范围设定为-200~-50 HU,手动分割LA-EAT,通过自动计算LA-EAT体积(图1)。

1.2.2 左房内电压标测 所有患者均首先行环肺静脉隔离术(pulmonary vein isolation, PVI),然后对于阵发性房颤患者直接进行左房内电压标测,如房颤仍持续存在则进行电复律,恢复窦律后进行标测。电压标测应用ST消融导管(美国强生公司)进行,取点时压力在5~30 g。双极标测电压低于0.5 mV定义为低电压[6]。



A B C

图 1 CTA 后处理所得心外膜脂肪图像

Figure 1 Epicardial fat images obtained after CTA postprocessing

A: the yellow area represents LA-EAT, and the volume is calculated by Volume software; B, C: the distribution of left atrial epicardial adipose tissue under multiplanar reconstruction (green represents fat). CTA: computer tomography angiography; LA-EAT: left atrium epicardial adipose tissue.

1.3 评价指标

收集患者基本临床资料、超声以及影像相关指标。根据电压标测结果,分为低电压组($n=56$)与非低电压组($n=190$)。

1.4 统计学处理

采用 SPSS 24.0 统计软件进行数据分析。符合正态分布的计量资料用均数±标准差($\bar{x}\pm s$)表示,采用 t 检验;非正态分布的计量资料,用中位数(四分位数间距)[$M(Q_1,Q_3)$]表示,采用 Mann-Whitney U 检验。计数资料用例数(百分率)表示,采用 χ^2 检验。采用 Spearman 相关性分析确定 DR-FLASH 评分与 LA-EAT 体积之间的相关性。二元 logistic 回归分析纳入单因素分析中 $P<0.1$ 的变量,以确定左房低电压区域(low voltage zone, LVZ)的预测因素。但二元 logistic 回归分析有两个独立的模型,模型 1 带有 DR-FLASH 各项得分,模型 2 包含每个变量得分相加的 DR-FLASH 总分。采用受试者工作特征(receiver operating characteristic, ROC)曲线分析 DR-FLASH 评分、LA-EAT 体积及其联合预测 LVZ 发生的价值。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 患者一般特征

共纳入有症状性房颤患者 246 例,其中男性 166 例,女性 80 例;体质量指数(body mass index, BMI)为(25.3±3.0) kg/m^2;左心房内径(left atrial diameter, LAD)为(40.8±5.2) mm;LA-EAT 体积为(29.8±10.7) cm^3;DR-FLASH 评分为 2(1,3)分;阵发性房颤 143 例(58.1%),持续性房颤 103 例(41.9%)。

2.2 无低电压组和低电压组基线特征比较

两组患者 LAD 和 LA-EAT 体积比较,差异有统计学意义($P<0.05$);相较于非低电压组,低电压组中 DR-FLASH 评分较高、女性较多,且持续性房颤较多,差异均有统计学意义(均 $P<0.001$)。其余指标比较,差异无统计学意义(表 1)。

表 1 两组患者一般资料比较

Table 1 Comparison of baseline data between two groups

Item	Non-LVZ group ($n=190$)	LVZ group ($n=56$)	P value
Age[years, $M(Q_1,Q_3)$]	61(53,67)	65(57,70)	0.018
Female[n(%)]	51(26.84)	29(51.79)	<0.001
BMI(kg/m^2, $\bar{x}\pm s$)	25.41±2.95	24.98±3.28	0.346
PersAF[n(%)]	66(34.76)	37(66.07)	<0.001
Hypertension[n(%)]	79(41.58)	21(37.50)	0.585
CAD[n(%)]	41(21.69)	13(23.21)	0.855
DM[n(%)]	22(11.58)	12(21.43)	0.061
Hyperlipidemia[n(%)]	34(17.89)	7(12.50)	0.341
eGFR[ml/(min·1.73m^2), ($\bar{x}\pm s$)]	101.66±17.73	100.26±19.24	0.609
CRP(mg/L, $\bar{x}\pm s$)	2.52±3.14	2.67±5.55	0.793
LAD(mm, $\bar{x}\pm s$)	40.35±4.67	42.18±6.47	0.020
LVEF(%, $\bar{x}\pm s$)	59.42±6.96	57.97±8.08	0.190
DR-FLASH[points, $M(Q_1,Q_3)$]	2(1,3)	3(2,4)	<0.001
LA-EAT(cm^3, $\bar{x}\pm s$)	27.90±9.87	36.27±11.00	<0.001

LVZ: low voltage zone; BMI: body mass index; PersAF: persistent atrial fibrillation; CAD: coronary artery disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; LAD: left anterior descending artery; LVEF: left ventricular ejection fraction; LA-EAT: left atrial epicardial adipose tissue.

2.3 单因素和多因素 logistic 回归分析

单因素 logistic 回归分析显示,年龄越大、女性、持续性房颤、较大 LAD、较高的 DR-FLASH 评分和较大的 LA-EAT 体积可预测 LVZ 的发生($P<0.05$)。在多因素二元 logistic 逻辑回归分析模型 2 中,LA-EAT 体积及 DR-FLASH 评分仍为 LVZ 独立预测因素($P<0.05$);模型 1 中,只有女性和持续性房颤与 LVZ 的存在独立相关($P<0.05$;表 2)。

表2 LVZ多元logistic回归分析

Table 2 Multivariate logistic regression analysis of LVZ

Factor	Univariate analysis			Multivariate analysis model 1			Multivariate analysis model 2		
	OR	95%*CI*	*P* value	*OR*	95%*CI*	*P* value	*OR*	95%*CI*	*P* value
Age	1.034	1.003-1.067	0.033	1.013	0.977-1.051	0.484			
Female	2.927	1.583-5.412	0.001	4.070	1.987-8.333	<0.001			
BMI	0.953	0.863-1.053	0.345						
PersAF	3.659	1.951-6.860	<0.001	3.538	1.607-7.791	0.002			
Hypertension	0.843	0.457-1.556	0.585						
CAD	1.091	0.536-2.220	0.809						
DM	2.083	0.957-4.533	0.064	2.164	0.904-5.180	0.083			
Hyperlipidemia	0.655	0.273-1.572	0.344						
eGFR	0.996	0.980-1.012	0.608						
CRP	0.994	0.932-1.059	0.843						
LAD	1.073	1.010-1.139	0.021	1.036	0.996-1.043	0.071			
LVEF	0.973	0.935-1.013	0.190						
DR-FLASH	2.091	1.622-2.692	<0.001				1.824	1.390-2.394	<0.001
LA-EAT	1.083	1.048-1.119	<0.001	1.072	1.032-1.113	<0.001	1.048	1.013-1.085	0.007

LVZ: low voltage zone; BMI: body mass index; PersAF: persistent atrial fibrillation; CAD: coronary artery disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; LAD: left anterior descending artery; LVEF: left ventricular ejection fraction; LA-EAT: left atrial epicardial adipose tissue.

2.4 LA-EAT体积与DR-FLASH评分相关性

在简单线性相关分析中LA-EAT体积与DR-FLASH评分呈正相关($r=0.439$; $P<0.001$; 图2)。其中DR-FLASH评分0、1、2、3、4、5和6分及以上患者的例数分别为30例(12.2%)、62例(25.2%)、61例(24.8%)、44例(17.9%)、37例(15.0%)、10例(4.1%)和2例(0.8%),其对应的平均LA-EAT体积分别为:(22.9±7.6)cm^3、(26.3±9.1)cm^3、(28.5±8.9)cm^3、(33.3±10.5)cm^3、(36.6±12.0)cm^3、(36.0±10.7)cm^3和(48.21±3.4)cm^3。LA-EAT体积随DR-FLASH评分的增加而增加,DR-FLASH评分≥3分组LA-EAT体积显著高于评分<3分组[(35.3±11.2)和(26.5±8.9)cm^3, $P<0.001$]。而LA-EAT体积和BMI无显著相关性($r=0.112$, $P=0.079$; 图3)。

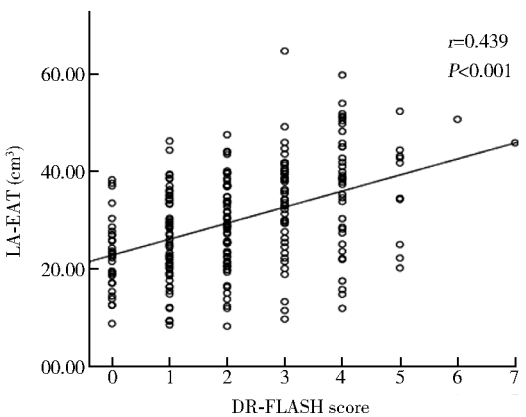


图2 LA-EAT体积与DR-FLASH评分相关性

Figure 2 LA-EAT and DR-FLASH score correlation

LA-EAT: left atrial epicardial adipose tissue.

2.5 LA-EAT体积与DR-FLASH评分对LVZ的预测价值

采用ROC分析确定LA-EAT体积与DR-FLASH评分作为预测LVZ的因素。LA-EAT体积(AUC=0.712, 95%*CI* 0.535~0.729; $P=0.008$),DR-FLASH评分(AUC=0.750, 95%*CI* 0.632-0.789; $P<0.001$)对LVZ有显著预测作用;LA-EAT体积和DR-FLASH评分相结合具有更高的预测价值(AUC=0.796, 95%*CI* 0.727~0.865; $P<0.001$; 图4)。

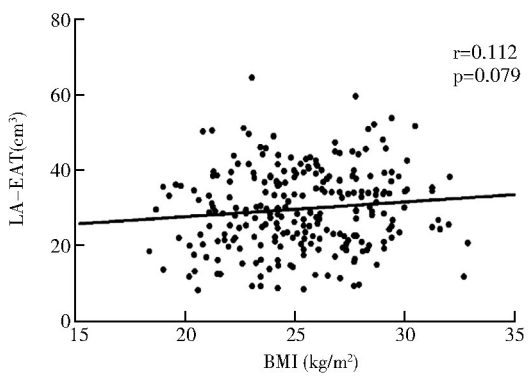


图3 BMI与LA-EAT体积的相关性

Figure 3 BMI and LA-EAT correlation

BMI: body mass index; LA-EAT: left atrial epicardial adipose tissue.

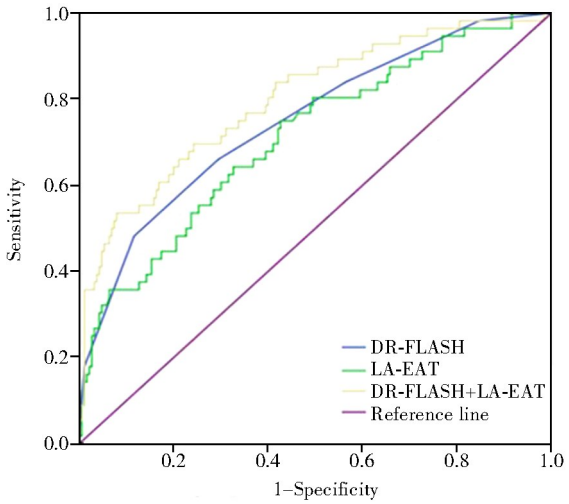


图 4 预测 LVZ 的 ROC 曲线

Figure 4 ROC curves for predicting LVZ

LVZ: low voltage zone; ROC: receiver operating characteristic; LA-EAT: left atrial epicardial adipose tissue.

3 讨 论

房颤是最常见的临床心律失常,它与心力衰竭和血栓栓塞的风险增加有关,导致病死率增加[1]。心房心肌的结构重构尤其是纤维化是房颤发病机制中的核心[7]。反映心房重构过程的 LVZ 也被称为电解剖底物,在房颤进展中发挥重要作用[8]。尽管 LVZ 的存在已被证明是导管消融术后心律失常复发的有力预测因子[9],但目前通过合适的临床和生物标志物等无创方法预测非瓣膜性房颤左房 LVZ 的研究依然是有限的。EAT 作为一种特殊的生物活性的内分泌组织,与心房(房颤底物)和肺静脉(房颤触发者)表面直接接触,并与心肌共同由冠状动脉供血[10],可通过无创的检查方法进行测量。基础研究已证实 EAT 可通过旁分泌及自分泌途径分泌多种促炎和抗炎脂肪因子,直接作用于邻近心肌,引起心房肌细胞纤维化[11]。

既往的研究发现 LA-EAT 的存在与较低的双极电压和作为电生理底物的碎裂电位有关[12,13]。本研究发现 LA-EAT 体积是左房低电压的独立危险因素,提示 EAT 在导致房颤发生的心房纤维化中发挥作用。既往研究发现 P 波持续时间、PR 间期[14]、左房功能和大小[15,16]、血液生物标志物 NT-proANP[17]等反应心房心肌病变的参数与心房心肌重塑相关。Ribo 等[18]发现较高的 CHA_2DS_2-VAS 评分与房颤导管消融后心房电压降低和更高房颤复发相关。另一项研究[19]报告显示,左房 LVZ 与 CHA_2DS_2-VASc 评分之间呈负相关,随着评分得分增加左房电压显著降低,但两种评分均未能预测左房 LVZ。DR-FLASH 评分包括作为首个针对预测心房基质而被开发的评分,是左房低电压存在的独立预测因素[20]。最近引入的 APPLE 评分,包括年龄>65 岁、持续性房颤、eGFR 受损[<60 ml/(min · 1.73m^2)]、左房内径≥43 mm 及 LVEF<50%,首次用于预测房颤导管消融术后房颤复发,而且 APPLE 评分也可显著预测 LVZ[21]。然而使用 DR-FLASH 评分预测电解剖底物价值最高,其发生左房 LVZ 的风险超过 2 倍[3]。本研究发现 DR-FLASH 评分是左房 LVZ 的独立危险因素,与以往的研究结果是一致的,但本研究中 OR 值较 Kosiuk 等[3]研究的 OR 值小,可能原因是本研究中患者平均年龄偏小,其 eGFR 通常大于 90 ml/(min · 1.73m^2),影响了评分的判定。同时 DR-FLASH 风险评分系统可能有一些局限性,与左房纤维化相关的包括氧化应激和炎症等各种生理和病理过程,并未在评分中体现。本研究首次发现通过加入 LA-EAT 体积可以弥补 DR-FLASH 评分系统的不足。研究结果证实,LA-EAT 体积随着 DR-FLASH 评分的增加而增加,且加入 LA-EAT 体积后提高了 DR-FLASH 评分系统的预测价值。另外,目前关于 EAT 与 BMI 的相关性研究并不明确,Erkan 等[22]的研究得出 BMI 和 EAT 之间没有相关性(r=0.13;P=0.082),与本研究结果一致。我们考虑存在以下可能:(1)BMI 只是衡量肥胖的一个参考值,它并不能准确地反映人体是否肥胖;(2)EAT 是一种特殊的内脏脂肪组织而 BMI 并不能明确区分体脂的分布,其相对能更好地反映皮下脂肪组织含量。

综上,本研究证实 LA-EAT 作为一种简便、无创、易测的生物标志物,可以弥补 DR-FLASH 评分系统的不足。通过术前 CT 测量心外膜脂肪体积并联合 DR-FLASH 评分,可以了解左房基质结构重构情况,制定更个体化的房颤消融策略及更密切的随访。

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