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功能性三尖瓣反流与右室–肺动脉耦联关系的研究进展

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摘　要

显著的功能性三尖瓣反流是心血管事件的独立预后因素，会导致右心重塑和功能障碍从而增加死亡率，并且死亡率及发病率与反流分级的增加也显著相关。近年来对于在出现严重右心室功能障碍之前进行早期干预这一观点重新引起临床医生的兴趣，对于三尖瓣反流如何干预以及何时干预仍是亟待解决的问题。功能性三尖瓣反流与右室功能、肺动脉负荷关系密切，右室功能适应持续增加的后负荷会维持右室–肺动脉耦联状态，而右心室重构不能适应变化的后负荷可导致其解耦联。因此，准确评估适应性向非适应性重构的转变时机对于对功能性三尖瓣反流患者的病情评估、临床决策、风险分层和预后判断具有重要意义。

关键词

三尖瓣，三尖瓣关闭不全，右室–肺动脉耦联，心室功能，右室重构

Research Progress on the Relationship between Functional Tricuspid Regurgitation and Right Ventricular-Pulmonary Artery Coupling

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Abstract

Significant functional tricuspid regurgitation is an independent prognostic factor for cardiovascular events, leading to right heart remodeling and dysfunction and thus increased mortality, also mortality and morbidity are significantly associated with increased regurgitant grading. In recent years there has been a resurgence of interest among clinicians in the idea of early intervention before severe right ventricular dysfunction develops. Thus, the question of how and when to intervene in tricuspid regurgitation remains urgent. Functional tricuspid regurgitation is closely related to right ventricular function and pulmonary artery loading; adaptation of right ventricular function to continuously increasing afterload maintains right ventricular-pulmonary artery coupling, whereas failure of right ventricular remodeling to adapt to changing afterload can lead to its uncoupling. Therefore, accurate assessment of the timing of the transition from adaptive to non-adaptive remodeling is important for condition assessment, clinical decision making, risk stratification, and prognosis in patients with functional tricuspid regurgitation.

Keywords

Tricuspid Valve, Tricuspid Insufficiency, Right Ventricle-Pulmonary Artery Coupling, Ventricular Function, Right Ventricular Remodeling

1. 引言

右室－肺动脉(right ventricle-pulmonary arterial, RV-PA)耦联是指右心室收缩力与右心室后负荷之间的关系。只有当右心室功能和肺血管阻力匹配时，正常的 RV-PA 耦联才能维持[1]。在疾病进展和慢性后负荷增加的过程中，右心室经历适应性重塑到非适应性重塑(RV-PA 解耦联)而心力衰竭。RV-PA 耦联良好能够确保右室负荷与肺动脉负荷之间能量传递的有效性，其测量的金标准是来自右心导管测压获得的右室压力－容积环(rightventricular pressure-volume loops, RVP-V loops)。但因其操作有创、复杂、难以广泛应用等缺点，促使临床研发了多种非侵入性超声心动图替代指标[2]。鉴于 RV-PA 耦联在心血管疾病的病理生理和发展进程中起到重要作用，评估耦联向解耦联的转变时机对三尖瓣反流患者的病情评估、临床决策、风险分层和预后判断具有重要意义。本文对现阶段功能性三尖瓣反流(functional tricuspid regurgitation, FTR)与 RV-PA 耦联关系的研究进展进行综述。

2. 右心室解剖及生理

左、右心室具有不同的胚胎起源，对应激的反应也不相同。一般而言，压力、容量超负荷或心肌病变均可导致 RV 功能障碍。当胚胎在子宫内发育时，RV 占总心输出量的 60%，此时左、右心室的壁厚相似[3] [4]。来自腔静脉氧合不良的血液由三尖瓣经 RV 进入 PA，由于此时肺血管阻力(pulmonary vascular resistance, PVR)较高，因此进入肺的血流量很少，高 PVR 状态使血液大都绕过肺部，经卵圆孔和动脉导管分流。这一现象在胎儿娩出发生了重要的生理转变，心脏结构和功能变化导致 PVR 迅速下降[5]。成人生理条件下，肺血管对血流的阻力非常低，因此，RV 与左心室(left ventricle, LV)不同，正常的 RV (无心

内分流情况下)心输出量与 LV 的心输出量相同，但其能量消耗却是 LV 的六分之一[6]。

从解剖学上看，RV 通常被认为由三部分组成：1) 入口或流入道，与体循环静脉回流相连，其由三尖瓣、腱索和乳头肌组成；2) 小梁状心尖部，通常壁薄；3) 出口或流出道，连接肺动脉的管状肌肉结构。结构上，正常成人 RV 薄壁呈新月形，而 LV 是厚壁，形似子弹。与左心室有三种不同的心肌纤维不同，右心室由浅(环向)纤维和深(纵向)纤维组成，浅表层(约占壁厚的 25%)主要由平行于房室沟方向环形排列，且与左心室表浅层心肌延续；深层心肌从房室沟向心尖呈整齐的纵向排列[7]。因此，由于其长轴上的三角形几何形状和短轴上的新月形形状，RV 不能有效的将收缩力集中于腔室中部。此外，RV 以蠕动运动的方式依次收缩，例如当流出道仍在收缩时，漏斗部已经处于收缩结束状态[8] [9]。经过 RV 的血流在穿过三尖瓣时依靠纵向与旋转运动来改变方向使其产生向心力，这种向心力在心脏收缩早期，将血液引导至室间隔方向，进而推动血液流向肺动脉瓣[10] [11]；RV 与 LV 不仅通过间隔而且通过心外膜环向肌细胞和心包间隙紧密相连，所有这些构成了双心室收缩和舒张相互依赖的解剖学基础。但与 LV 相比，RV 更依赖于纵向缩短，并且更受负荷条件的影响。

3. FTR 患者右室-肺动脉耦联的病理生理

3.1. 右室－肺动脉耦联病理生理

大量研究已经证明 RV 收缩性能与其所受后负荷密切相关[12] [13] [14]，右室后负荷实际上是右室收缩力与肺动脉顺应性、阻力和反射波相互作用的结果，在功能正常的右室中，这两个部分是“耦联的”[15]。因此在疾病的发生发展过程中，二者作为一个整体共同评估更为合理[16]。右室－肺动脉耦联确保了右室负荷与肺动脉负荷之间能量传递的有效性，从而将血液转运至肺动脉。当最大心输出量(cardiac output, CO)以最小的能量消耗转移到肺循环时，此时偶合最佳。

肺小动脉、肺毛细血管和肺静脉收缩、增生或肺动脉闭塞引起的 PVR 增加可引发肺动脉高压，进而导致右心后负荷增加[17] [18] [19]。虽然 RV 无法良好的适应压力负荷的急剧增加，但在慢性压力超负荷作用下 RV 早期发生适应性重构，防止心肌过度拉伸以维持心室形状。随着持续的压力超负荷，心肌收缩力不再增加以匹配超载后负荷时，自适应耗尽，RV 向适应不良表型转变[2]，进行性右室扩张和非同步化以维持每搏量与心输出量，心肌细胞在各种病理状态下，表现为应激状态，细胞胶原含量以及胶原表型将发生改变，心肌间质纤维胶原增加和沉积，心肌出现纤维化从而导致心肌僵硬[20] [21]。既往研究表明，RV 慢性压力超负荷改变心肌纤维结构，是造成右室收缩不良的主要因素，并最终导致右室功能的恶化[22] [23] [24]。随后右室非适应性重构即 RV-PA 解耦联，将发生明显右心衰。

3.2. 右室重构与 RV-PA 耦联

RV 纤维化从适应性到非适应性重构转变的确切时机仍亟待明确。一方面，胶原纤维可增强心肌，适应性地维持结构并防止超负荷条件下的进一步扩张，从而维持适当的心脏收缩模式并保持 RV-PA 耦联；另一方面心肌纤维化使室壁僵硬度增加，顺应性下降，最终损害心肌功能，导致 RV-PA 解耦联[25]。此外,关于心肌结构影响器官功能的机制仍不确定，组织学研究认为 RV 纤维化是肺动脉高压晚期的特征，然而这些研究主要依靠终末期肺动脉高压患者的心肌活检，此时的心脏重塑和纤维化不能反映疾病的早期和代偿阶段的情况。利用无创影像技术能够在病程的早期对患者进行检查，间接评估纤维化的非侵入性成像方法，MRI 是心肌纤维化成像的金标准，基于超声斑点追踪技术的心肌应变也是替代指标[26]。

3.3. FTR 的 RV-PA 耦联

FTR 与 RV 重构相关，包括右心室机械功能受损、扩张，最终导致收缩功能障碍；也与三尖瓣环和

右房扩张相关。FTR、RV 重构和右房扩张这三者构成恶性循环，一旦开始，很难中断[27]。FTR 患者预后是由右心室对负荷增加的反应决定的[28]，而 RV-PA 耦联可用于评估右室收缩力是否能够匹配后负荷的变化以及右室负荷与肺动脉负荷能量传递的有效性[29]。压力超负荷可能是 FTR 患者 RV-PA 解耦联的主要决定因素：左心疾病和肺动脉高压是 FTR 的最主要病因，增加的肺动脉压(即右室后负荷)会在纤维、组织和器官水平进行性右心室重塑，导致右心室纵向拉伸和球形变形，进而发生三尖瓣叶栓系和 FTR 的发展[30]。与之不同，由于房颤导致的右房与三尖瓣环扩张引起的 FTR 主要通过改变右室容量负荷[31]，容量超负荷可能导致壁张力增加，心肌纤维化和 RV 结构改变，直接导致 RV 收缩力受损，从而 RV-PA 解耦联[32]。因此，RV-PA 解耦联代表了 FTR 中慢性 RV 压力和容量超负荷的最终结局。

4. RV-PA 耦联检测手段

4.1. RV-PA 耦联的有创检查手段

由于 RV 收缩性能与前、后负荷直接相关，因此评估 RV-PA 耦联需分别独立测量右心收缩功能与后负荷。目前，通过有创侵入性右心导管测压所得的 RVP-V loops 仍是检测 RV-PA 耦联的金标准[33]。评估 RV 收缩功能指标为收缩末期弹性(end-systolic elastance, Ees)，通过右心导管记录多个 RVP-V loops 同时降低前负荷(降低前负荷可以通过在下腔静脉中放置充气球囊或通过 Valsalva 动作)来测量，通过每个单独环路的收缩末期压(end-systolic pressure, ESP)的直线斜率即为 Ees。评估后负荷为动脉弹性(arterial effective elastance, Ea)，即 ESP 和每搏量(stroke volume, SV)的比值。RV-PA 耦联被量化为收缩末期压力与动脉弹性之间的比率(Ees/Ea) [34] [35]。但为了避免前负荷对其的潜在影响，Inuzuka 等[36]开发了评估单次心动周期收缩力的方法，其研究表明与多心动周期测量有较好的一致性。研究显示最佳 Ees/Ea 值介于 1.5 和 2.0 之间[37] [38]，然而解耦联发生的确切时机仍不明确。Tabima 等研究正常与高血压小鼠模型认为 Ees/Ea < 0.5 与右室－肺动脉解耦联相关[39]。临床试验中 Tello 等认为 Ees/Ea < 0.8 可预测肺动脉高压患者即将发生右心衰竭[40]。Schmeißer 等的研究显示 Ees/Ea < 0.68 与右心室扩张/重塑和功能障碍相关，并与短期和中期显著增加全因死亡率相关[41]；其他相关研究如 Hsu 等[42]证实截断值 0.65 预示着临床恶化时间更短。

4.2. 超声对 RV-PA 耦联的无创评估

尽管右心导管是评估 RV-PA 耦联的金标准，但由于其具有侵入性、耗时、昂贵且应用不广泛，在分析和解释复杂数据方面需要经验，很少被应用。因此已经研发了多种非侵入性超声心动图替代指标。最早描述和最有效的无创多普勒超声心动图获得的替代性指标之一是三尖瓣环平面收缩期位移(tricuspid annular plane systolic excursion, TAPSE)和估计肺动脉收缩压(pulmonary arterial systolic pressure, PASP)的比值(TAPSE/PASP) [43]。相关研究与金标准 Ees/Ea 测量值进行对比验证，结果显示 TAPSE/PASP 临界值 0.31mm/mmHg 与 RV-PA 解耦联和右心衰竭相关[44] [45]。目前相关研究也通过不同的超声心动图参数替代 TAPSE 成为 RV-PA 耦联其他无创替代物，如外侧三尖瓣环的收缩期组织峰值速度、右心室面积分数变化、基于斑点追踪的右心室游离壁纵向应变和整体纵向应变，甚至三维右室射血分数等[2] [46] [47]。几乎所有这些公式都依赖于反流速度和右心房压力对 PASP 的估计，但这两者在严重 TR 的情况下都可能不准确[48]。近期，Gavazzoni 等提出了一个新的 RV-PA 耦联参数，定义为 RV 正向 SV 除以三维右室舒张期容积，将负荷压力转化为容量，临床结果证实在单变量和多变量回归模型中，新指标 RV 正向 SV 除以三维右室舒张期容积与主要终点的相关性比其他 RV-PA 耦联指数更强[49]。

5. RV-PA 耦联在 FTR 患者中的应用

TAPSE/PASP 已被证明与有创血流动力学密切相关，并能够预测心血管疾病的结局，如肺动脉高压、

射血分数降低的心力衰竭、射血分数保留的心力衰竭和重度主动脉狭窄[12] [50] [51]。2022 年 ESC/ERS 更新的肺动脉高压诊治指南中，将 RV-PA 耦联纳入超声评估的右心功能指标，也使得对肺动脉高压患者右心功能评估更加全面[52]。尽管这些心血管病变可能与显著 TR 共存，但尚未在显著 FTR 患者队列研究中广泛研究 RV−PA 耦联的预后价值。尽管已经证实 RV-PA 耦联和 FTR 存在病理生理学相互作用，但对其临床影响知之甚少。近年来随着对 FTR 的深入研究以及介入治疗的蓬勃发展，对 FTR 的研究也逐步增多。Yoshida 等[53]通过构建小鼠模型验证大量 TR 的存在或导致 Ea 被低估。因此，在严重 TR 的情况下，Ees/Ea 被高估，这可能导致对 RV 功能受损的低估。Sugiura 等[29]通过评估 RV-PA 耦联及其对接受二尖瓣经导管缘对缘修复术患者 TR 临床结果的影响，提出 TR 的临床影响根据 RV-PA 耦联的程度而变化的设想。该研究中值得注意的是 TR 等级越高，临床风险越高，因此也提出一个新的概念框架：即 TR 的预后由两个关键因素决定，TR 和 RV-PA 耦联的严重程度，但仍需要更多的研究来证实这两个参数的对疾病预后的影响。Fortuni 等[15]纳入 1149 名 FTR 患者的一项 20 年大型回顾性队列研究提出 RV-PA 解耦联是唯一与全因死亡率独立相关的超声心动图参数($P < 0.001$)；并且 FTR 患者的 RV-PA 解耦联与不良预后独立相关，能够改善风险分层。由此可见，RV-PA 耦联在 FTR 患者的风险分层、临床结果预测和指导治疗中起着关键作用，但仍需更多研究支持。

6. 展望

随着超声心动图技术的不断发展，希望在未来能够取代有创检测成为 RV-PA 耦联评估的首选方法。现阶段仍需要大量前瞻性研究来明确超声无创技术评估 RV-PA 耦联向解耦联转变的最佳应用参数或进一步利用运动负荷超声心动图来揭示 RV-PA 耦联对 FTR 患者进行风险分层方面的作用以及其在预测 FTR 预后中的价值，以帮助临床医生更好地评估、管理患者病情，并对治疗方案进行更精确的调整，以改善患者的生活质量和预后。

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