EHRA/HRS/APHRS/SOLAECE 心房心肌病专家共识：定义、特征和临床意义

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前言和心房心肌病的定义

心房对心脏功能具有重要作用[1,2]。除了对心室充盈的影响外，心房还作为容量储备、自主起搏细胞和心脏传导系统的重要部分（例如窦房结、房室结），并分泌调节液体稳态的钠尿肽如心房利钠肽（ANP）和脑钠肽（BNP）。心房肌受到许多心脏和非心脏因素影响[3]，并且，在某些方面比心室肌更敏感[4]。除了三条特殊传导束[5,6]，心房还可通过工作心肌细胞激活，因此心房肌任何结构和构型上的变化均可能导致明显的电生理紊乱。此外，心房细胞（心肌细胞和非心肌细胞成分，如成纤维细胞样细胞，内皮细胞和神经元）对病理刺激的反应敏感而广泛，并易受到一系列遗传因素的影响[7]。其反应包括心房肥厚和收缩功能减退、致心律失常的心肌细胞离子通道和转运功能改变，心房纤维母细胞增生，神经过度再生和血栓形成的变化[2]。因此，心房病变对心脏功能、心律失常发生和卒中风险均有重要影响[1,8]。

已经对心室心肌病进行了很好的分类；然而，文献中缺少对心房心肌病的定义和详细分析。这一专家共识报告由代表欧洲心律协会（EHRA）、心律学会（HRS）、亚太心律学会（APHRS）以及拉丁美洲心脏起搏和电生理学会（SOLAECE）的工作组制定，其目的是定义心房心肌病，并回顾相关文献，研究心房心肌病对心律失常管理和中风的影响。

心房心肌病的定义

工作组提出了以下心房心肌病的工作定义：“任何影响到心房的构型、结构、收缩或电生理的复杂病变，并可能产生相关临床症状”（**表 1**）。

已知许多疾病（如高血压、心力衰竭、糖尿病和心肌炎）或情形（如衰老和内分泌紊乱）引起或导致心房心肌病的发生。然而，产生的变化并不一定属于疾病特异性，对于病理变化通常有许多相似性[9,10]。病理变化的程度可能随时间和心房中的位置不同而不同，导致许多个体内和个体间的差异。此外，一些病理过程对心房的影响可能具有高度选择性（如，心房颤动诱发的重构），大部分影响心房的心肌病也会或多或少地对心室产生影响。目前没有被接受的心房病理学的组织学分类。因此，这里我们提出的是工作中应用的心房心肌病的组织学/病理学分类方案（**表 1，图 1**）。我们使用 EHRAS（EHRA/HRS/APHRS/SOLAECE）的缩写定义四个分类：（Ⅰ）以心肌细胞病变为主[11-15]；（Ⅱ）以纤维化病变为主[10,14,15]；（Ⅲ）同时存在心肌细胞病变/纤维化病变[9,11,12]；（Ⅳ）以非胶原浸润病变为主（伴或不伴有心肌细胞变化）17-19。这一简单分类可能有助于表述在不同临床状况下的主要的潜在病理学变化。在某一患者中，EHRAS 分类可随时间变化，并且在不同的心房部位可能不同。因此，这一分类仅仅是描述性的，并不与其他分类方法相矛盾（NYHA 分类，CCS 分类等），从 EHRAS 分类Ⅰ类到 EHRAS 分类Ⅳ类并不表示严重程度的进展（**表 2**）。这一分类可能有助于描述活检中的病理学改变，以及由影像技术等得到的与病理学变化相关的结果。在将来，这有助于确定心房颤动（AF）的个体化治疗目标（**图 1-3**）。

表 1 心房心肌病的定义

任何影响到心房的构型、结构、收缩或电生理的复杂变化，并可能产生相关临床症状。

解剖学特征和心房肌结构

正常心房结构

大体形态学

心房均包括心房体部和心房耳部（**图 4**）。在体部，有包括体循环或肺静脉（PVs）口的静脉成分，以及围绕心房流出道的前庭部分[20]。房间隔（IAS）分隔心房体部。左心房（LA）的静脉结构定位于后上方，接受四个角的肺静脉，形成突出的心房顶部。与被倾斜的 IAS 分隔的右心房相比，LA 定位更靠后上方[21]。

LA 耳部（LAA）比右房耳部（RAA）小。LAA 较狭窄且形状不同，开口于心房体部，并覆盖于左冠状动脉回旋支上。其内膜上存在复杂的肌嵴和膜网络[22,23]。LAA 的形态学差异已有描述，并表明 LAA 形态学与血栓形成的风险相关[24]。

Bachmann 束是沿着两侧心房前壁走行的宽肌束（**图 4**）。右侧支向上延伸至窦房结，向下至右侧房室沟，而左侧支混入较深的肌纤维，穿过 LAA 颈部，向后再进入 LA 前庭周围。LA 壁厚度不一致（1-15mm），比右心房厚[25]。

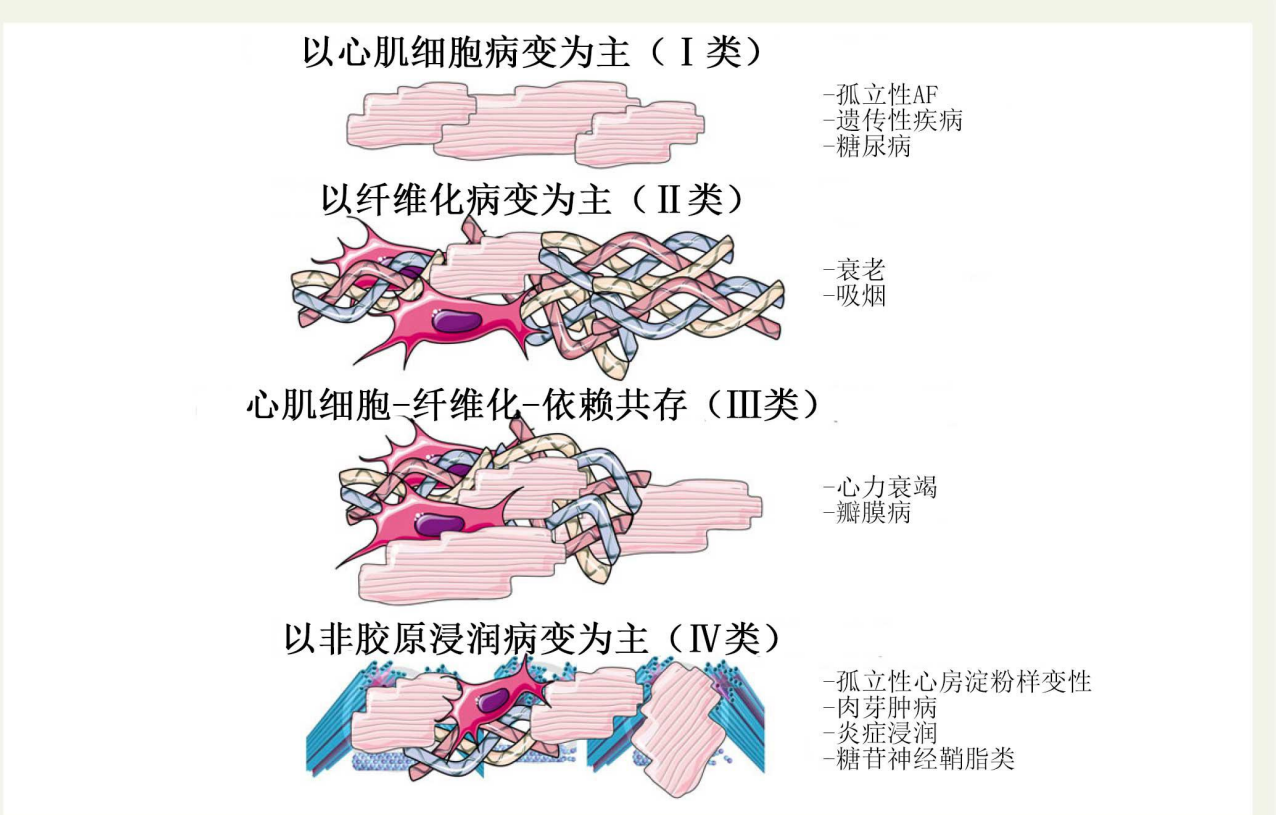

图1 ：心房心肌病的组织学和病理学分类（EHRA/HRS/APHRS/SOLAECE）：EHRAS分类。EHRAS分类可能随不同病因不同时间而变化，也可能在心房不同部位存在差异。值得注意的是，该分类仅仅是描述性的。EHRAS分类并不用于描述疾病从EHRAS Ⅰ类-EHRASⅣ类的进展。

正常心房肌

心房肌细胞

心房肌细胞是几何结构复杂的圆柱体，有时其末端有分叉，在此处通过带状的闰盘与相邻的纤维连接。这种具有收缩性的合胞体，呈带状结构，导致心房冲动非均一性的各向异性传导[9,11,26]。在光镜下仅能明确心房和心室肌细胞在大小上的形态学差异[27]。在石蜡包埋的人体标本中，LA 心肌细胞横径大约为 12mm，而心室肌细胞为 20-22mm[11,28]。心房肌细胞主要为单核细胞；小部分具有两个或两个以上的核。细胞核通常位于中央，具有颗粒和（或）凝聚染色质。核的形状受纤维收缩的影响，纵向拉伸形成梭形[29]。生物化学方面，与心室肌细胞相比，心房肌细胞含有更多脂质[30]。

在细胞核、收缩装置、细胞骨架以及细胞器方面，心房肌细胞和心室肌细胞有很多共同点[27,29,31,32]。不同于心室肌细胞，心房肌细胞没有广泛的 T 管网络，但是有突出的肌浆网结构，被称为 Z 管[33]。因此，心房肌纤维膜不突出于细胞，电压依赖性 Ca^{2+}通道功能主要在细胞外周[34]。心房肌细胞的特殊颗粒（100－400 nm）主要位于毗邻高尔基体的核周区，其中含有 ANP、BNP 及相关肽[23,24]。

表 2 心房心肌病的 EHRAS 分类

EHRAS 分类	组织学特征
Ⅰ[11-15,503]	主要影响心肌细胞的形态学和分子病变，有细胞肥大和肌细胞溶解；没有明显的病理上的组织纤维化或其他间质病变
Ⅱ[8,12,14,504-505]	以纤维化病变为主；心肌细胞外观正常
Ⅲ[9,11,12,217,266]	心肌细胞病变（如细胞肥大，肌细胞溶解）和纤维化病变共存
Ⅳ[17-19]	间质基质的改变而没有显著的胶原纤维累积
Ⅳa	淀粉样物质沉积
Ⅳf	脂肪浸润
Ⅳi	炎症细胞
Ⅳo	其他间质病变

心房间质

心房间质包括细胞内和细胞外成分（见**图 2-5**）。细胞内成分包括成纤维细胞/肌纤维母细胞、脂肪细胞、未分化间充质细胞和孤立的炎性细胞。心房壁上有许多中等大小的血管，尤其是在心外膜下。在心房肌中，常可发现成熟的脂肪细胞组织，尤其是在心外膜，并且常常渗透到冠状动脉分支壁内。脂肪细胞的数量十分不同，且随年龄增长而增加[27]。细胞外成分由形成心肌骨架主体的胶原纤维、粘蛋白颗粒、脂类碎片、球形微粒和基质囊泡构成[27]。

胶原纤维，主要是Ⅰ型，是正常且必需的组分（**图 1-5**）。心房纤维组织可被细分为纯间质性的和血管周围的（或动脉外膜的）。间质胶原纤维大约占心房壁体积的 5%。稀疏的节后神经末梢也位于心房肌（心脏自主神经系统），主要分散在脂肪垫内，但在心肌细胞中也存在[35]。

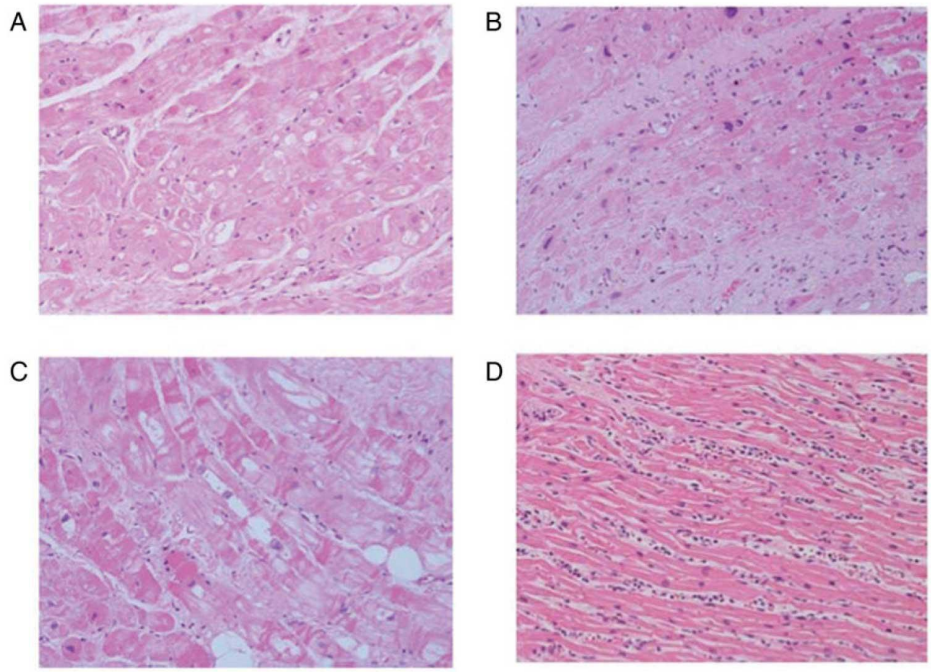

图2 ：（A）EHRAS Ⅰ类（活检）：主要影响心肌细胞的明显病变，有细胞肥大和肌细胞溶解；与心肌细胞病变相比，纤维化不太明显。（B）EHRAS Ⅱ类（活检）：与严重纤维化病变相比，心肌细胞病变相对较轻；在这一病例中，间质病变比心肌细胞病变更普遍。（C）EHRAS Ⅲ类（活检）：心肌细胞病变和胶原纤维沉积共存。（D）EHRAS Ⅳ类（尸检心脏）：主要为嗜中性粒细胞心肌炎。

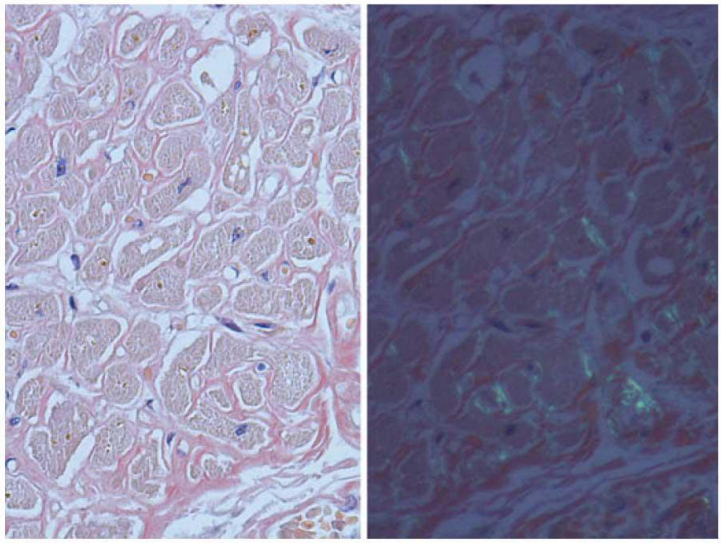

图3 ：EHRAS Ⅳ类（尸检心脏）：图片显示带有一些纤维的心肌间质，但是主要为淀粉样蛋白（AL型）沉积（左图，刚果红染色，普通光镜；右图，刚果红染色，偏振光显微镜）。

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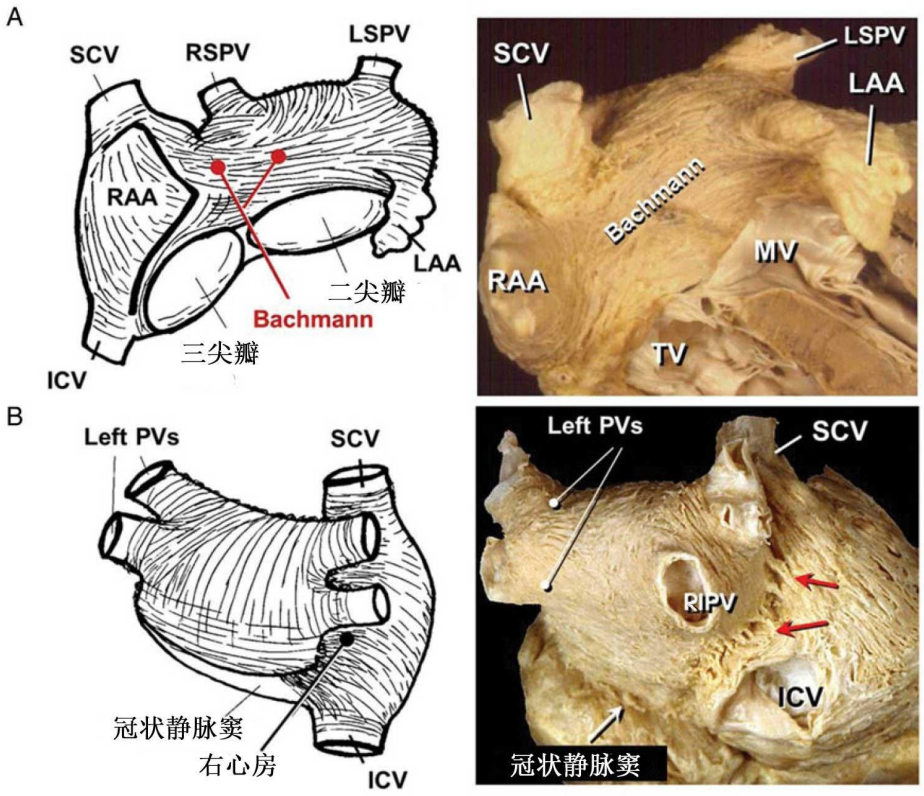

图4：示意图和心脏解剖图显示在心房壁上表浅部位心肌束的排列。（A）前面观：显示房间肌束Bachmann束及其分支，左侧支和右侧支。（B）左右心房顶部和后壁观：右肺静脉（PVs）通过腔静脉后方区域。外膜剥离后显示纤维方向的突然变化和在左、右肺静脉之间区域的心肌束（间隔肺静脉束）。红箭头指示连接两侧心房的多个肌束；ICV：下腔静脉；LAA：左房耳；LSPV：左上肺静脉；MV：二尖瓣；RAA：右心耳；RIPV：右下肺静脉；RSPV：右上肺静脉；SCV：上腔静脉；TV：三尖瓣（详见正文）。

心房特异生理学和功能学

心房选择性电生理特征

心房有许多不同于心室的电生理特征，这决定了其心律失常易感性。

动作电位/离子通道特征

心房肌细胞有着不同于心室肌细胞的独特动作电位（AP）特征，这其中很大一部分来自于独特的离子通道特征和分布（**图 6A**）[36,37]。心房背景内向整流 K^+电流（I_{K1}）比心室 K^+电流小，导致静息电位负值较小，且复极 3 期斜率更为平缓。心房细胞有两种在心室细胞中不存在的 K^+电流：超速延迟整流电流（I_{Kur}）和乙酰胆碱敏感 K^+电流（I_{KAch}）。此外，有证据表明心房 Na^+电流具有与心室电流不同的特性[38]。正如心房和心室 AP 不同，心房不同部位也存在不同的 AP 和离子通道特征[37,39]。这些细胞电生理学特征影响抗心律失常药物的作用和设计，也可能影响对房性心律失常和疾病的反应[36,37]。

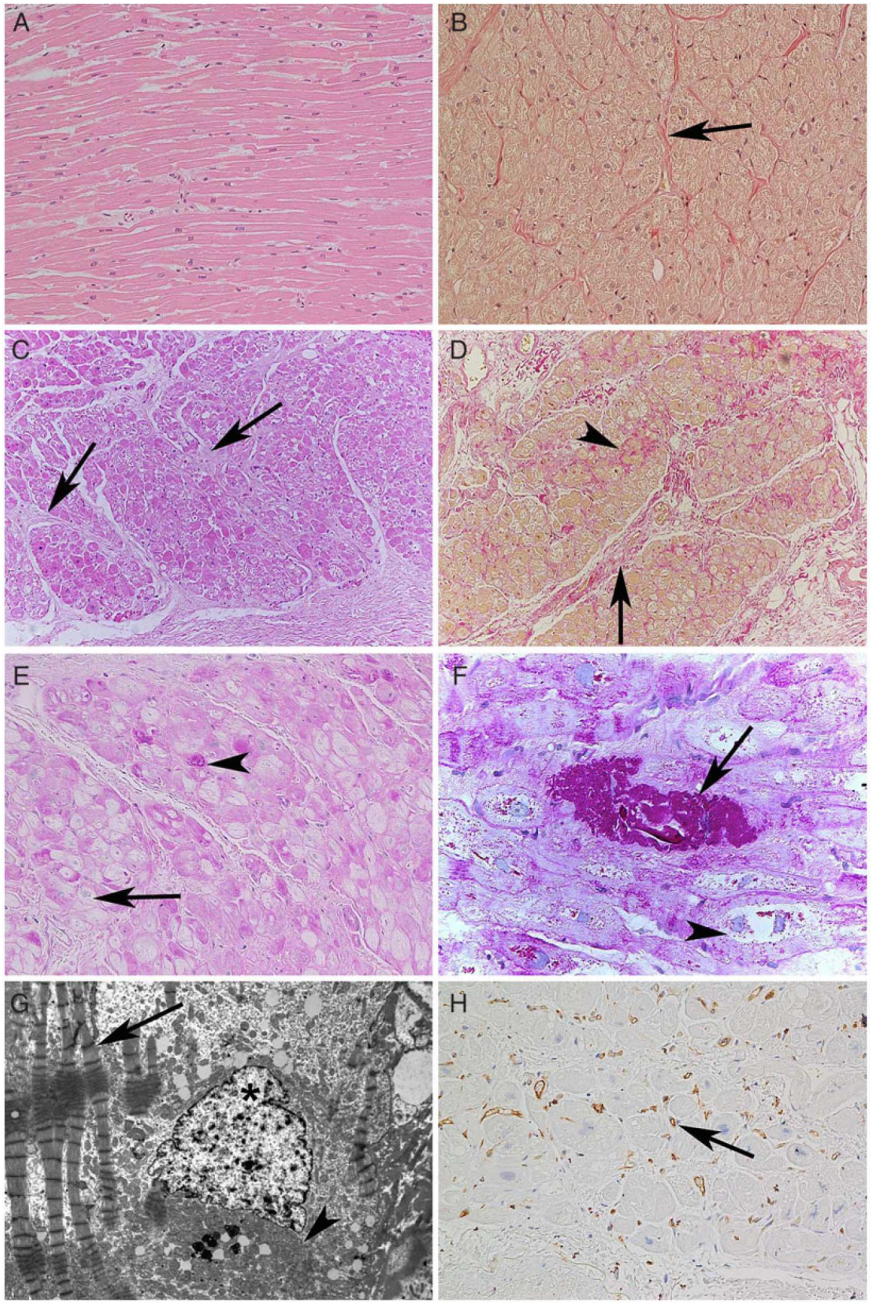

图5：左心房的正常组织形态和二尖瓣疾病相关房颤的病理改变。（A）中倍镜视野下由均质心肌细胞构成的大型条带组成的正常左心房心肌。（B）与（A）同一心房，万吉森染色显示胶原纤维（红色）主要见于血管外膜（箭头）。（C）低倍镜视野，来自于二尖瓣疾病相关心房颤动患者的心房。心肌细胞的大型条带被大量病理性纤维组织分隔（箭头）。（D）与（C）同一心房，万吉森染色显示血管周围的病理性纤维明显增厚（血管周围纤维，箭头），并将心肌细胞分为独立的或小群体（间质纤维化，短箭头）。（E）心房颤动中，大量的心肌细胞自核周区开始丧失收缩成分，导致所谓的心肌溶解。这些区域可能是中空的（箭头）或充满糖原（锲状箭头）。（F）高倍视野下同时伴有糖原富集（箭头）和中空的心肌细胞的细胞溶解。（G）伴有细胞周围明显的收缩组分丧失（星号）的细胞溶解的超微结构。在空泡区域，线粒体常有积聚，而相邻的肌原纤维呈现不正常收缩征象（箭头）。（H）心房颤动患者的LA，心肌微循环（箭头）轻度减少，并呈不规则分布。染色 （A和C）苏木红染色；（B和D）万吉森胶原染色；（E和F）过碘酸雪夫染色；（G）超微结构影像；（H）抗CD31抗体免疫组化分析。
原始放大倍数：A，B，E，和(H)×20；(C和 D)×4；(F)×40；(G)×2800

细胞间偶联特征

心房细胞间偶联蛋白（连接蛋白）的模式与心室肌中分布不同[36]。工作心室肌细胞仅表达连接蛋白-43，

心房肌细胞主要表达连接蛋白-40（**图 6B**）[36]。连接蛋白-40 分布的异质性常见于阵发性 AF，并可能在其中起到病理生理作用[40]，遗传变异影响连接蛋白-40 序列和（或）转录并使其对 AF 发生易感[41]。

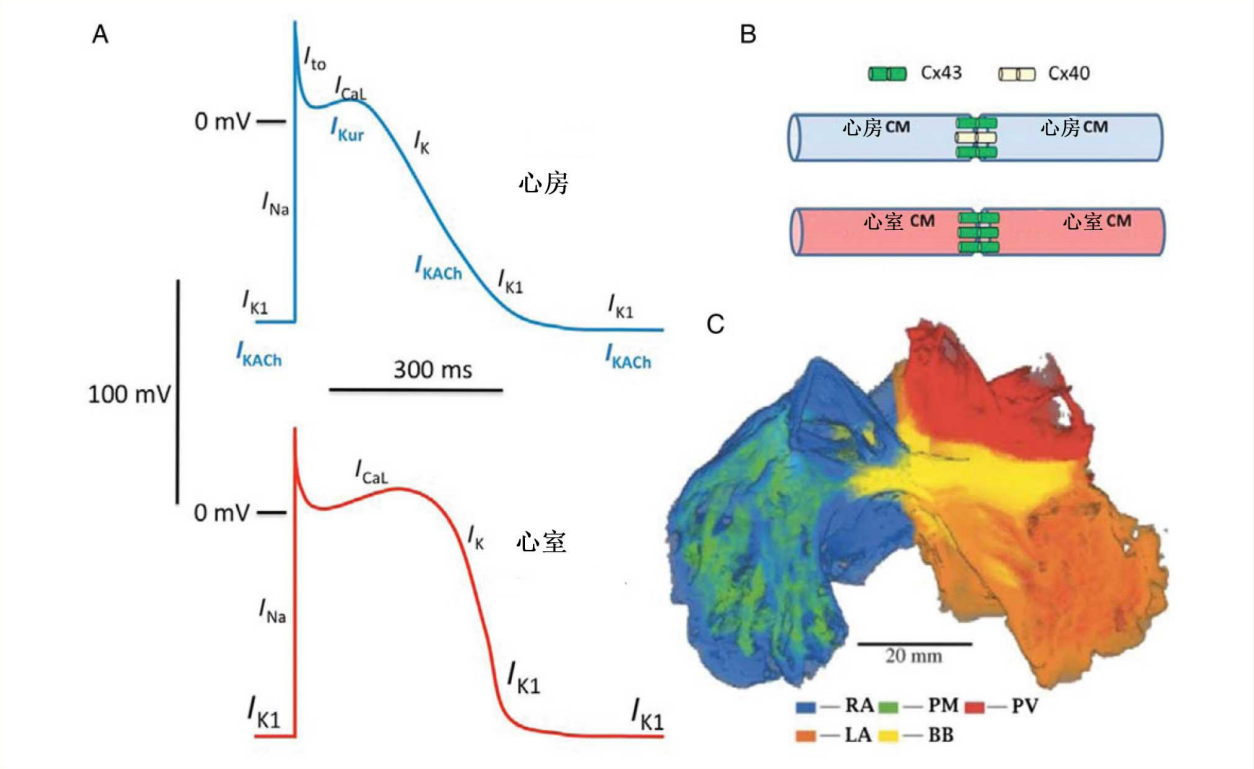

图6 ：（A）心房和心室动作电位特征和基础离子流的比较。心室肌与心房肌细胞相比，静息电位（-mV）更负，心室（平均-80至-85mV）vs心房（-70至-75mV）。（B）在心房和心室中，连接蛋白分布不同，心室肌细胞（CMs）仅表达连接蛋白-43，但是心房CMs同时表达连接蛋白-40和连接蛋白-43。（C）绵羊心房结构的现实重建。右心房（RA），左心房（LA），梳状肌（PM），Bachmann束（BB）和肺静脉（PV）以不同颜色标记。经允许引自参考文献（43）。

心房结构特征

心房有十分复杂的 3D 结构（**图 6C**），这在心室中并无发现。包括心房间连接仅局限于 Bachmann 束、间隔和 CS；在右心房内，梳状肌、终末嵴和纤维围绕冠状窦；在 LA 内，起源复杂的纤维围绕着 PVs。这些结构上的复杂性对心房病理生理学和房性心律失常治疗有着重要的潜在影响[42]。近年来在对如此复杂的几何结构的现实数学重建上做了大量工作[43]，这些已被纳入旨在实现特定患者的心律失常治疗的分析方法中[44]。诸如梳状肌和终末嵴等心房组织的条带样排列，使得其传导主要为纵向传导，其“各向异性比值”（纵向/横向传导速率）高达 10，而工作心室肌的典型比率在 2-4 之间[45]。

自主神经节

心脏表面有自主神经节，是心脏自主神经控制的重要节点[46]。此外，心脏局部神经支配和心内自主反射的变化在生理学和心律失常控制中起着重要作用。大多数心脏自主神经节位于心房，尤其是在 PVs 口区域。因此，它们对这一区域的心房活动产生重要影响，尤其是对 AF，并且如 PVs 消融等治疗手段可能通过改变自主神经节而影响抗心律失常治疗的效果[42,46,47]。

左心房结构

左心房对心血管系统整体性能的贡献是由独特因素决定的。首先，左心房功能是左心室（LV）充盈的重要决定因素。其次，心腔的特异结构、电和离子重构改变左心房功能和心律失常易感性。第三，心房功能与 AF 的治疗反应高度相关。第四，LA 容积是反映 LV 舒张功能减退的程度和持续时间的重要生物学标记。发展测定 LA 大小和功能的先进非侵入性指标可能有助于临床上利用 LA 功能在预后和危险分层中的重要性[1,48]。

两个薄肌层的纤维方向（其肌束起源和终止均在房室环）对功能分析来说是一种复杂的挑战。超微结构上，与心室相比，心房肌细胞直径更小，T 管更少，高尔基体更为丰富。此外，收缩和松弛，传导速度和各向异性差异，以及肌球蛋白亚型复合体、离子转运通道的表达和缝隙连接蛋白均存在不同（见相关章节）。

左心房功能

LA 的主要作用是调节心室充盈以及心血管性能，这些功能是通过作为 LV 收缩期间 PV 回流的储存容器、LV 舒张早期 PV 回流的通道以及 LV 舒张期间作为增压泵增加 LV 充盈实现的。在这些心房功能和心室收缩舒张性能之间存在着重要的相互作用。因此，LA 顺应性（或是僵硬度）影响程度较小，在 LV 收缩期间 LA 收缩性和舒张性是储备功能的决定因素，收缩期中 LV 收缩末期容积和 LV 基底的下降是主要的影响因素。传导功能也受到 LA 顺应性和与储备功能的相互关系的影响，但是因为二尖瓣在舒张期开放，传导功能也与 LV 顺应性（主要由松弛度决定）密切相关。心房增压泵功能反映了心房收缩的强度和时间，但是也取决于静脉回流（心房前负荷）、LV 舒张末期压力（心房后负荷）和 LV 收缩期储备。

左心房增压泵功能

左心房增压泵功能是由心房收缩所增加的 LV 充盈（到 PVs 的最小逆向射血），可由以下指标估测（1）有或无有效心房收缩时的心输出量；（2）使用频谱多普勒测定的经二尖瓣、PV 和 LA 耳血流反映的相对 LV 充盈；（3）LA 缩短率和容积分析；（4）左心房体部的组织多普勒和形变分析（应变和应变率成像）[1]。增压泵功能也可由超声通过估测 LA 收缩产生的动能和收缩力来评价。LA 收缩对 LV 充盈和心输出量的重要性仍存在争议。基于 LA 的压力和体积之间的瞬时关系分析 LA 收缩负荷的独立指数，类似于 LV 收缩末期弹性模量的测量，已被用来作为独立测量 LA 泵功能的指标，并在体外和活体犬中进行了验证（**图 7**）[49]。然而，在人体中，可通过侵入性或半侵入性方法得出 LA 压力-容积环[50]，这些方法繁琐、耗时且难以实施。心肌应变和应变率的测定反映了心肌变形的强度和程度，组织多普勒速率（组织多普勒成像，TDI）或 2D 超声心动图（2D 斑点追踪或 STE）技术（**图 8**）提供对 LA 心肌性能和收缩性的客观、无创的测量指标，且克服了上述限制[1,51]。

左心房储备功能

在 LV 收缩时，几乎一半的 LV 每搏输出量和其相关的能量是储备在 LA 中的。这些能量随后在 LV 舒张期消耗。储备功能很大程度上受到心室收缩期间左心房顺应性的影响，这通过严格的拟合一定心房压力和容积范围内的二尖瓣开放/关闭以及心室舒张期时的心房压力和内径，形成指数方程来计算[52]。尽管这一方法需要心房内径和压力，但也可通过简单的 PV 多普勒估测心房储备功能：在心室收缩期 LA 血流流入的比例提供了心房储备功能指标。正如最大射血分数或扩张性分数，储备功能也可由 LA 时间-容积关系来估算，先由最大 LA 容积减去最小 LA 容积来计算，再分别用最大或最小 LA 容积进行校正。

尽管在很大程度上被忽略，但是 LA 耳部比 LA 体部顺应性更好[52]，因此 LA 耳部对 LA 整体顺应性影响很大，在二尖瓣手术中行常规心房耳部切除/结扎具有潜在的负面影响。

在 LV 收缩期左心房应变和应变率能够预测 DC 复律或 AF 消融后转复为窦性心律成功性，作为心房纤维化和结构重构的替代指标，同时也可估测心房压力（例如跨二尖瓣 E/E'），应变性具有非侵入性估测心房扩张性的潜能[1,53]。

左心房的通道功能

左心房的通道功能主要发生在心室舒张期，代表不能归因于储备功能或增压泵功能的血容量的输送，大约占心房血流量的 1/3[54]。在 LA 通道功能和储备功能间存在相互关系；这些功能的再分配是重要的代偿机制，有利于心肌缺血、高血压性心脏病以及二尖瓣狭窄（MS）时的 LV 充盈。通道功能可通过舒张早期跨二尖瓣血流、舒张期 PV 血流和舒张早期的 LA 应变和应变率评估。

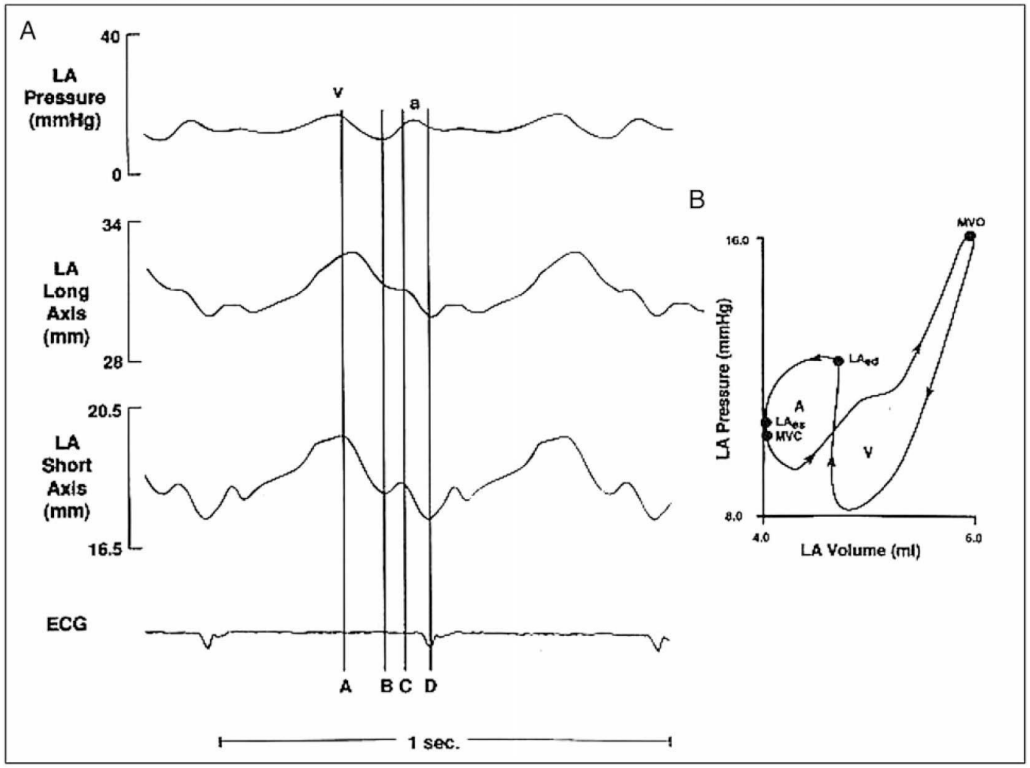

图7：左心房压力-容积环。（A）左心房压力和内径的时域模拟记录。垂直线为二尖瓣开放时间（A），心房被动排空末期和心房舒张期开始（B），心房舒张末期（C），心房收缩末期（D）。a和v代表各自的静脉压力曲线。（B）一次搏动的左心房压力-容积环呈特征性的8字形。箭头表示作为时间函数的环的前进方向。A环表示心房收缩活动。V环表示LA被动充盈和排空。MVO：二尖瓣开放时间；MVC：二尖瓣关闭的大致时间；LA：左心房收缩末期；LAd：左心房舒张末期。经许可转自参考文献（49）。

心房特异性 Ca^{2+}调控

在心房和心室 Ca^{2+}调控蛋白的表达和功能上存在明显不同（**图 9**）[55]。心房心肌细胞收缩和舒张时间缩短，且 Ca^{2+}瞬变持续时间较短[56-58]。心房中，与心室相比，SR Ca^{2+}-ATP 酶 2a（SERCA2a）蛋白水平和活性增高两倍，但 SERCA2a 抑制剂受磷蛋白（PLB）较少[57,59]。心房，而不是心室，SERCA2a 也受肌脂蛋白（SLN）调节，去除 SLN 增加心房 SRCa^{2+}摄取和收缩性[60]。L 型 Ca^{2+}流[61]在心房和心室中相似，而 2 型兰尼碱受体蛋白、隐钙素、三联蛋白、连接蛋白和 Na+-Ca^{2+}交换蛋白水平在心房中比心室中低[59,62,63]。与心室肌相反，心房肌中 T 管较少[64]。此外，与心室肌细胞相比，心房肌细胞拥有更多的钙缓冲线粒体[56]。因此，

心房 Ca^{2+}波开始于细胞外周部分，并向细胞中心扩布，激活 SR 中其他的 Ca^{2+}位点[55]。

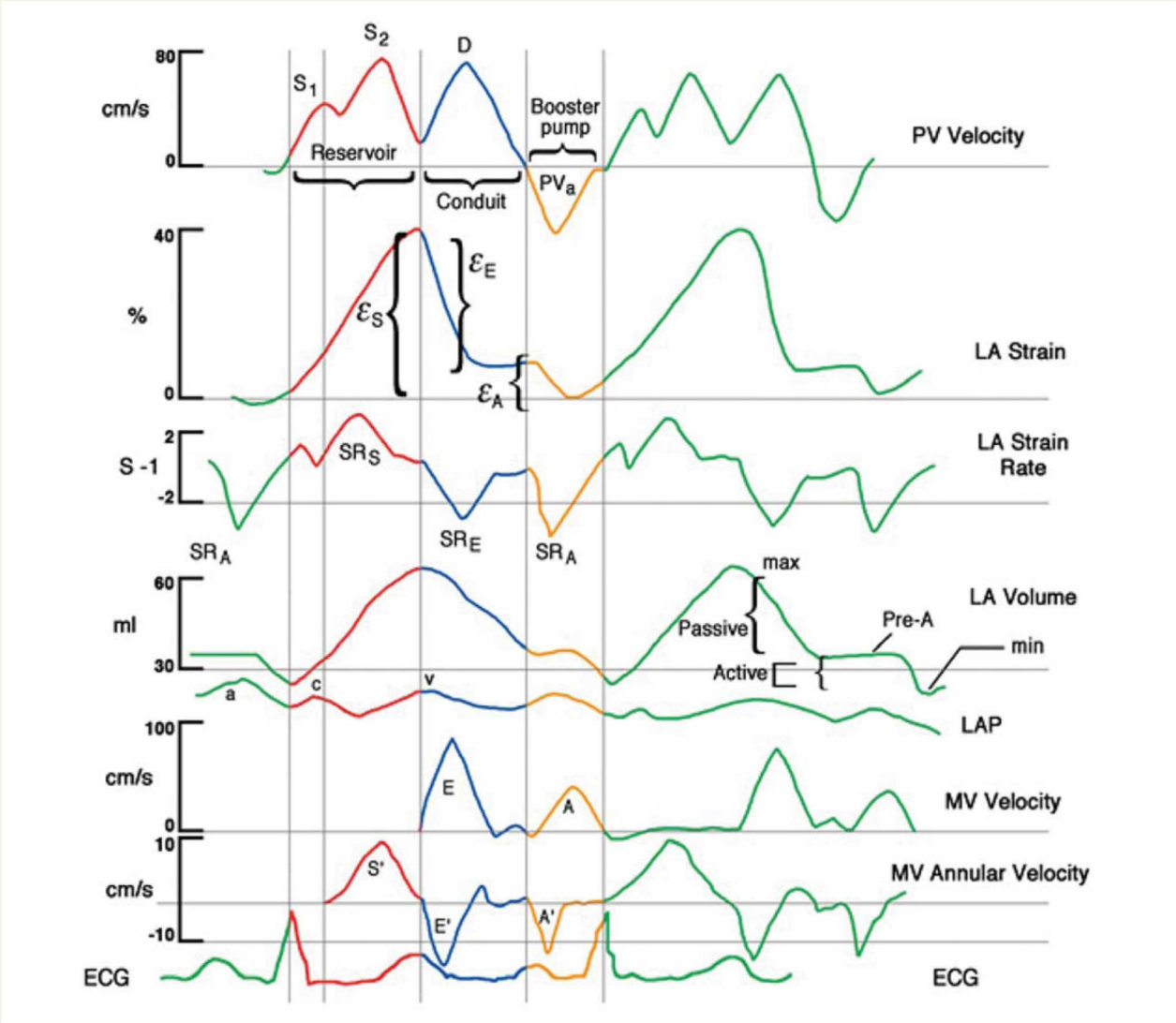

图8：LA函数颜色标记显示了心脏循环中相关的心房功能（红：储备；蓝：通道；黄：增压泵）。显示的是肺静脉（PV）流速，LA应变，LA应变率，LA容积和压力以及二尖瓣频谱和组织多普勒。经许可转自参考文献（1）。

心房心肌病的病理学

孤立性心房纤维化（不伴有 AF）

当没有明显可解释的或潜在合并疾病能够识别时，诊断为“孤立性”心房颤动（LAF）[65,66]。在过去一些年里，出现了 AF 相关的新的流行病学资料，真正的 LAF 病例数量正在逐渐减少[67]。正如 AF 伴随的疾病一样，LAF 在男性中比女性中更为多见，其比例为 3-4:1[68]。近期的研究显示真正被诊断为 LAF 的病例甚至可超过 60 岁，因此这一年龄限制似乎过于保守[69]。同时，尚不清楚是否左心房扩大的病例应当从 LAF 中排除。实际上，LA 扩大可能正是心律失常的结果[70]。

“孤立性”心房颤动血栓栓塞的风险较低，大约 15 年的累计中风风险仅为 1-2%[66]。然而，随着年龄和（或）心血管合并疾病的增加，AF 相关并发症的风险（包括血栓栓塞事件）增加[71]。最初被诊断为 LAF

的患者，在其不同左心房容积的基础上可能发生不同的临床过程：长期随访中 LA 大小均保持正常的个体显示有相对良性的临床过程，而 LA 扩大的个体经历了诸如卒中、心肌梗死和心力衰竭等负性事件[72]。LAF 患者中的大多数首先表现为阵发性发作，较少发展为永久性 AF[71,73]。

心房颤动有明确的遗传因素[7]。包括预测强度较低的常见的基因变异和具有更强外显性的罕见基因突变[7]。

Frustaci 等[14]研究了 孤立性阵发性 AF 患者右房间隔活检标本的组织形态学，发现了慢性炎症浸润、心肌局灶坏死、局部纤维替代和与肌溶解一致的细胞胞浆空泡。在 12 名患者中，有 10 名具有 EHRASⅢ类病变，2 名具有 EHRAS Ⅱ类病变。Stiles 等[74]在阵发性 LAF 患者中发现了双心房结构变化、传导异常和窦房结功能障碍。Skalidis 等[75]证实了心房灌注异常和冠状动脉血流储备受损。最近，对持续或长期持续性 LAF 患者的 LA 后壁的活检标本的形态测定评估证实，与对照组相比其心肌细胞肥大、心肌溶解、间质纤维化和连接蛋白-43 表达下降[76]。

孤立性心房淀粉样变性

不溶性错误折叠蛋白的积累与年龄相关的退行性疾病数量增加相关[77]。淀粉样变性是不溶性纤维蛋白在β折叠结构中的沉积，特点为与刚果红等染料结合。最常见的形式是局限于心房的年龄相关或老年淀粉样变性，是已知孤立性心房淀粉样变性的一种情况（IAA）[17,78]。心房淀粉样变性的发生率随年龄增加，在 90 岁年龄段超过 90%[79]。孤立性心房淀粉样变性也与结构性心脏病相关。在接受心脏外科手术的 167 名患者的心房活检标本中，26 个淀粉样蛋白阳性的样本中有 23 个来自于风湿性心脏病（RHD）患者，而其余 3 个为房间隔缺损[80]。总体发生率为 16%，远高于来自于外伤受害者的心房尸检标本的对照组（3%）。组织学上，IAA 为 EHRASⅣa 类（**图 3，表 2**）。

心房钠尿肽是形成 IAA 的纤维源性蛋白[81]。在大多数患者中，淀粉样蛋白沉积是对 ANP 的免疫反应[17]，而甲状腺素运载蛋白，一种与全身性老年淀粉样变性相关的转运蛋白占 10%[4]（在其他研究中发现为 NT-pro-ANP[82]）。随着纤维化进展，淀粉样变性可引起局部传导阻滞，IAA 中 P 波时限增加。与窦性心律相比，心房淀粉样变性在 AF 患者中更为常见（**图 3**）。AF 和 IAA 均随年龄增加而增加，且在女性中多见，但是这两种疾病之间的关系与年龄和性别无关[83,84]。孤立性心房淀粉样变性在 80%的老年患者的 PV 肌袖中可检测到[84]。

组织特异性淀粉样变性，如阿尔茨海默病中，没有检测到纤维沉积的量与疾病进展之间的关系[85]。相反，疾病表型与可溶性纤维蛋白前体聚合物的积累关联最为密切[86]。淀粉样蛋白前体寡聚物（PAOs）对心肌细胞具有细胞毒性[87]。它们不能与刚果红结合，因此不能通过标准的淀粉样物质染色方法显示。使用构象特异性抗体，在 92 名接受心脏外科手术的无房颤的患者中，74 例心房标本中检出 PAOs，常与 ANP 相伴在同一部位出现[88]。淀粉样蛋白前体寡聚物含量与高血压无关。需要更多研究进一步证实这种关联，以及 PAOs 是否在 AF 中增高。

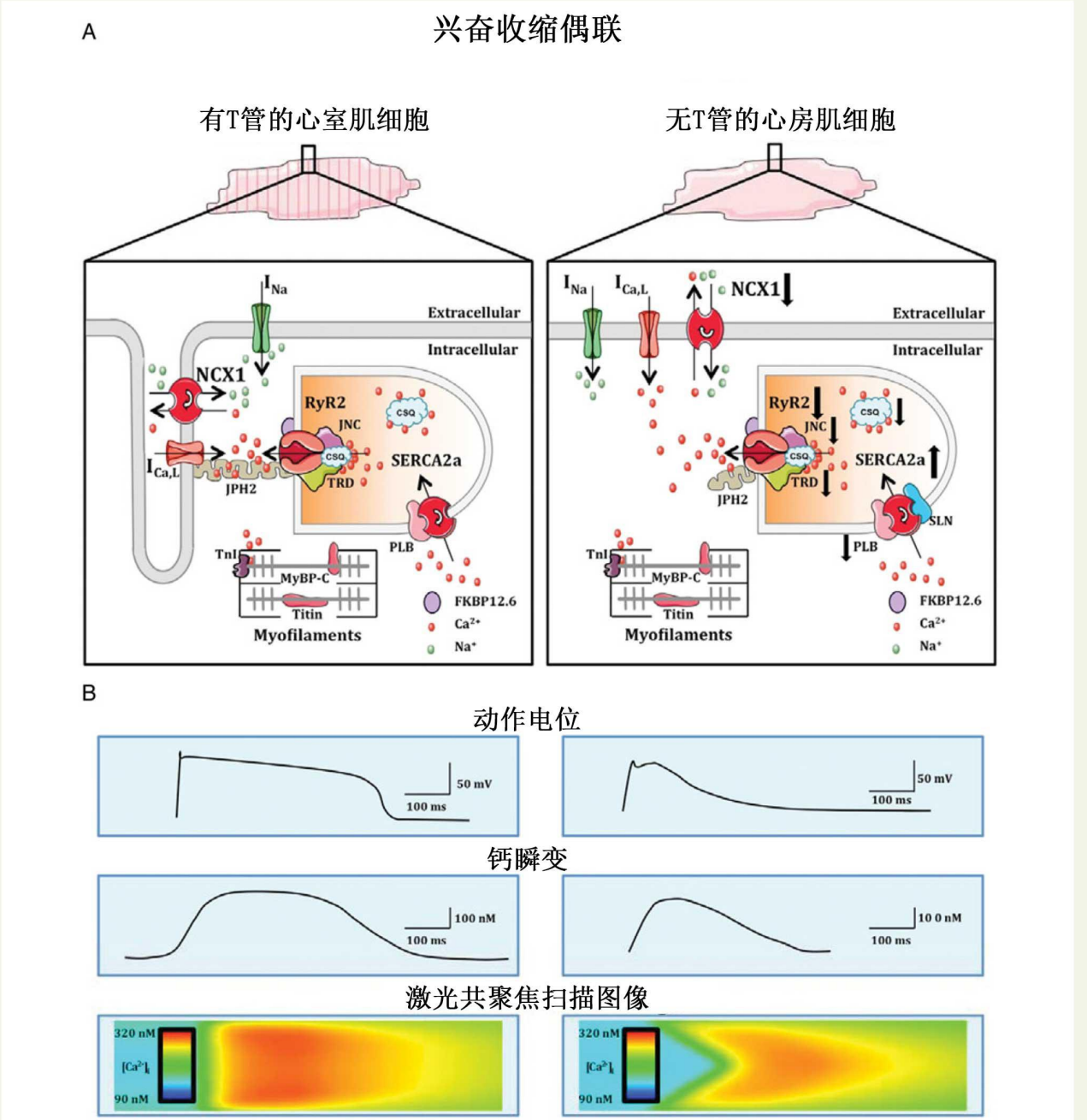

图9：心房和心室的兴奋-收缩偶联。细胞的结构和主要的Ca^{2+}调控蛋白示意图，以及相关的电流和离子转运蛋白（A）。动作电位图解（顶部），Ca^{2+}瞬变（中间）以及心室（左侧）和心房（右侧）心肌细胞细胞内Ca^{2+}波向细胞中心形扩布的激光共聚焦扫描图像（底部）（B）。箭头指示心房和心室肌细胞中Ca^{2+}调控蛋白表达和/或功能的差异。INa^{+}：Na^{+}电流；FKPB12.6：FK506-结合蛋白12.6；JPH2：连接蛋白-2；MyBP-CMyosin结合蛋白C；TnI：肌钙蛋白I；更多的缩写见正文。

NPPA 突变

心房钠尿肽由心房释放，是心房对心房牵张和容积扩张的反应，产生利钠、利尿和血管扩张作用[89]。它还与其他内源性系统相互作用，抑制肾素-血管紧张素Ⅱ-醛固酮和交感神经系统，并调节离子流[90,91]。心房钠尿肽敲除小鼠会出现心肌肥厚和对压力应激反应过强的情况[92]。编码 ANP 前体蛋白的基因 NPPA，其编码的 ANP 前体（prepro-ANP）为含有 151 个氨基酸的蛋白质，信号肽切除后形成 pro-ANP[93]，储存在心

房致密颗粒中。释放的 pro-ANP 经水解蛋白处理生成 N 末端-pro-ANP 和 ANP，长度分别为 98 和 28 个氨基酸。N-末端-pro-ANP 剪切为三种激素，其生物学活性与 ANP 相似，分别为：长效钠尿肽激素（LANH），血管扩张肽和利钾尿激素。

遗传研究表明 ANP 异常导致家族性房性心动过速和心房心肌病。在一个 Holt-Oram 综合征的大家系中，T 盒转录因子 5（TBx5）的错义突变导致伴有早发 AF 的不典型表型和包括 NPPA 在内的多个基因的过表达[94]。在一个多位成员有早发 LAF 的大家系中，确定了 2 个碱基缺失，导致 ANP 终止密码被废除，产生含有通常的 28 个氨基酸再加上 12 个氨基酸残基的异常 C-末端的成熟蛋白质[95]。在受突变型影响的家族成员中，ANP 血浆浓度比野生型 ANP 浓度高 5-10 倍。对 ANP 的电生理效应的研究不一致[96]。

其他 NPPA 变异（S64R 和 A117V）也与 AF 相关[97,98]。S64R 变异发生于血管扩张肽而不是 ANP。含有这种突变的截断肽使 I_{Ks} 增加几倍，预测其效应为缩短动作电位时程（APD）[97]，但是在不受影响没有 AF 的老年人中也发现了这种变异[96]，其功能病理学意义仍然未知。

晚近，在存在预计会损伤蛋白质结构的 NPPA 突变（Arg150Gln）的患者中描述了一种常染色体隐性遗传性心房心肌病[99]。其表型特征为双心房扩大，早期伴有 AF 和心房扑动等房性心律失常[100]。双心房扩大逐渐进展，最终导致严重心房静止，伴有进展性心房电压降低和心房瘢痕扩大。心房结构改变是原发性，或是继发于心房扩大仍属未知。在这些患者中 ANP 抗肥厚效应的丧失可能引起明显的心房扩大。

遗传性肌营养不良

常见遗传性肌营养不良累及心脏，与伴有脂肪或纤维替代的心肌细胞变形有关（**表 3**）[101-103]。在一些病例中，这可以是首先出现或主要的临床表现。多个复合体和途径参与维持肌细胞的完整性，蛋白组分的缺陷或缺失可导致进展性细胞死亡。大量的抗肌萎缩蛋白－糖蛋白的复合体在细胞外基底膜与心肌细胞的细胞骨架形成连接。由于抗肌萎缩蛋白、肌聚糖和其他复合体相关蛋白质的病变，最突出的表现是由于弥漫性心肌受累以及继发于 LV 功能障碍的心律失常和传导异常的扩张型心肌病[101-105]。特别是当累及心房时可导致窦房结病变和/或伴有血栓栓塞事件的房性心律失常[106,107]。Ⅰ型营养不良性肌强直是成人肌营养不良的最常见类型[108]。在 10 年随访中高达 15%出现房性心律失常[109]。传导异常和房性心律失常存在是猝死的独立危险因素[103,110]。在 Emery-Dreifuss 肌营养不良和肢带型肌营养不良Ⅰ B 型中，广泛的心房纤维化可导致心房静止[101]。在 Emery-Dreifuss 肌营养不良中，可观察到伴有缓慢心室反应的 AF 和心房扑动以及心搏停止，并且伴有血栓栓塞和卒中[111]。在面肩肱型肌营养不良中，心律失常罕见，多是室上性心动过速[112]。组织学上，其组织成分可能不同，包括了所有的 EHRAS 类别（见**表 2**）。

由于充血性心力衰竭所致心房心肌病

充血性心力衰竭（CHF）是 AF 的常见原因（促发条件）[3]。CHF 诱发的心房表型是复杂的。其中特别重要的因素是心房纤维化，在试验模型中，CHF 的早期即可发生，这在很大程度上，至少部分是由于心房心室成纤维细胞表型差异造成的[4]。充血性心力衰竭相关纤维化进展缓慢，至少，促进 AF 的基质主要是纤维化进程而不是诸如离子流或连接蛋白改变等其他心房组分的重构。不同于 AF 诱发重构的病例，CHF 中的心房离子流改变不缩短 APD 或是引起整体传导减慢[113,114]，因此对心律失常发生没有直接贡献。另一方面，CHF 心房由于 Ca^{2+}调控异常易于产生触发活动[115]。主要的潜在异常是细胞内 Ca^{2+}超载增加。然而其根本机制仍不完全清楚，这似乎涉及到受磷蛋白超磷酸化（增加 SR Ca^{2+}摄取）和 AP 延长（通过增加 L 型 Ca^{2+}通道开放时间而增加此期间的 Ca^{2+}负荷）。CHF 诱发的 Ca^{2+}调控异常最终的表型产物是由于舒张时 Ca^{2+}从 SR 释放异常引起的局部异位激动，与阵发性和长程持续性 AF 中所见异常相似[116]。

尽管细胞质内钙瞬变增加，但充血性心力衰竭时心房收缩功能下降，这表明对细胞内钙的收缩敏感性降低，这可能是因为总的和磷酸化的肌球蛋白结合蛋白 C 表达减少[115]。在有 CHF 的 AF 患者中，低收缩力

可能对血栓栓塞事件可能性增高是重要的。CHF 中的心房改变，许多在心室也能看到。然而，高度选择性的心房纤维化可导致心房心肌病，但对心室功能无明显影响，尤其是在之前有 CHF，而经治疗缓解基础病因之后代偿良好的患者中。CHF 中胶原沉积明显，大多是引起 EHRAS 分类中Ⅱ类和Ⅲ类的特征。然而，EHRASⅣi 类和Ⅳf 类在心房的某些部位也可发现（见**表 2**）。

表 3 累及心脏的遗传性肌营养不良

肌营养不良	蛋白/基因	原发心脏病
Duchenne 肌营养不良	抗肌萎缩蛋白	DCM
Becker 肌营养不良	抗肌萎缩蛋白	DCM
Ⅰ型营养不良性肌强直	DMPK	CSD
Emery-Dreifuss 肌营养不良	Emerin	CSD
	核纤层蛋白 A/C	（DCM）
肢带型肌营养不良	核纤层蛋白 A/C	CSD
	肌聚糖	CM
	其他	
面肩肱型肌营养不良	Dux4	CSD（罕见）

阻塞性睡眠呼吸暂停

已知阻塞性睡眠呼吸暂停（OSA）损害心脏功能并促发 AF[117-119]。阻塞性睡眠呼吸暂停延长心房传导时间，减慢心房传导，降低心房电图电压，增加心房电图复杂性[117,118]。OSA 增加信号平均 P 波时间，这在持续正压通气治疗后明显减少[120]。在大鼠模型中，重复阻塞型呼吸暂停超过 4 周，增加 AF 易感性，并通过改变连接蛋白-43 和诱发心房纤维化减慢心房传导[121]。

心房颤动诱发心房重构

心房颤动本身诱发心房重构，这有利于 AF 的维持、发展和稳定化[41,116]。快速心房率引起细胞内 Ca^{2+} 负荷增加。这通过潜在的 Cav1.2 亚单位下调和 I_{KAch} 组分激活增加诱发 $I_{Ca\text{-}L}$ 降低[41,116,122,123]。随着 Cav1.2 翻译的抑制和 Ca^{2+}依赖性蛋白酶的激活，MiR-328 上调，引起 L 型 Ca^{2+}通道蛋白分解故障[41,116]。Ca^{2+}/钙神经素/NFAT 介导的 miR-26 抑制物下调导致 I_{K1} 频率依赖性上调，去除了对 Kir2.1 的翻译抑制作用[41,116]。I_{K1} 增加通过缩短心房肌细胞 AP 以及使其超极化从而使 AF 稳定化[41]。小电导钙激活 K^+（SK）电流（I_{SK}）在 AF 中也有作用[41,116]。计算模型显示慢性心房颤动（cAF）中总的内向整流 K^+电流增加是缩短 APD 并使静息膜电位超极化从而使折返环稳定化的主要因素[41,116]。

房性心动过速重构通过不同机制减少钙瞬变波幅，从而促进心房收缩功能受损[41,116,124]。心房收缩性降低引起心房“顿抑”，这可能与血栓栓塞并发症相关。

在几个动物模型中，长期房性心动过速重构引起传导减慢，至少部分是因为 I_{Na} 下调[122]。由于连接蛋白重构导致的缝隙连接解偶联的不均一分布可能有助于心房传导减慢[41,116]。连接蛋白-40 分布不均一与反复猝发起搏诱发 AF 的山羊中 AF 的稳定性相关[125]。在 AF 相关重构的犬 PVs 中连接蛋白-40 表达降低，可能是

由于与心动过速诱发的钙激酶引起的连接蛋白降解[41,116]。

长期房性心动过速/AF 本身可能引起心房纤维化，这又促进其长期持续[126]。快速心房电活动促进成纤维细胞通过自分泌和旁分泌途径分化为胶原分泌的肌纤维母细胞[32]。房性心动过速诱发的 NFAT 介导的成纤维细胞 miR-26 降低可能也有助于结构重构。心房成纤维细胞具有瞬时受体电位（TRP）家族的非选择性阳离子通道，携带 Ca^{2+}进入细胞；细胞内 Ca^{2+}增加触发胶原生成增加。由于 miR-26 抑制 TRPC3 基因表达，miR-26 降低增加 TRPC3 表达，促进成纤维细胞 Ca^{2+}进入，引起增殖/肌纤维母细胞分化[127]。TRPM7 可能与其相似，有助于 AF 中的纤维化改变[128]。

cAF 中 APD 缩短也是由于内向整流 K^+电流增加[129]，包括 I_{K1} 和 I_{KAch} 的一种构成形式[41,116]。在 AF 患者右心房中，由于潜在 Kir3.1 和 Kir3.4 亚单位降低，激动剂激活的 I_{KAch} 减少[129]，但非激动剂依赖电流增加[41,116]。

长程持续性 AF 的心房心肌病患者表现为自发舒张性 SR Ca^{2+}释放事件（SCaEs）以及延迟后除极（DADs）[130]。CaMKII 依赖 RyR2 超磷酸化是 SR Ca^{2+}渗漏和 SCaEs 的基础[32,106,130]。蛋白激酶 A 依赖的 RyR2 超磷酸化也有发生[130]，似乎促进 EKBP12.6 亚单位从 RyR2 通道的解离。较大的内向 NCX 电流可能也有增强 DADs 的倾向[130]。

尽管早期工作指出 AF 患者中 I_{Na} 或 Nav1.5α亚单位的 mRNA 表达没有变化，但近期研究报告 I_{Na} 峰值降低[41,116]。也有晚钠电流增加的证据，尽管其功能上的后果不太清楚。连接蛋白-40/43 的 mRNA 和蛋白水平变化可能也有助于 cAF 患者中折返促进的传导异常。连接蛋白-40 表达降低伴有细胞膜横向的偏侧化可能引起不均一传导[41,116]。

总之，离子通道改变有利于 AF 的稳定化和复律后的早期复发。Ca^{2+}调控异常与心房异位活动有关，在长期持续性 AF 到顽固性 AF 的进展中，心房纤维化是重要的。心房纤维化诱导的心房肌病存在依赖于 AF 持续时间的改变。持续很短的 AF 不产生超声上的改变，而 AF 持续几周即可引起 EHRAS Ⅰ类变化[13]。长期持续性 AF 产生 EHRAⅢ类变化[126]。

药物相关的心房颤动

很多种类药物均可诱发 AF，无论是在没有心脏病的患者还是之前有心脏病的患者（**表 4**）中[131]，但是药物诱发 AF（DIAF）未得到足够重视。DIAF 总体发生率仍然未知有以下几个原因：（a）与房颤相关的特异性药物的证据在很大程度上是基于无对照的报告，很少有对照的前瞻性临床试验；（b）DIAF 通常是阵发性的，难以记录到或记录很少；（c）如果在 i.v.药物后很快发生，DIAF 则容易被识别（如腺苷或多巴酚丁胺），如果在暴露于多重药物后出现 AF 发作，则记录有可能被错过；（d）患者通常接受多重药物治疗，很难确定特异性的“罪犯”药物；（e）使用非心血管药物，DIAF 通常由非心脏病学家作出诊断，常常对心律失常事件和临床病史描述不清[132]。有多重机制解释 DIAF 的发病机制：（a）直接的心房电生理效应，如缩短不应期，减慢传导，或由于 Ca^{2+}负荷引起的触发活动；（b）自主神经张力变化；（c）心肌缺血；（d）直接的心肌损伤和其他机制，如促炎症细胞因子释放，氧化应激，低血压和电解质紊乱[131,132]。

在大多数病例中，DIAF 是一种良性自限性疾病。然而，在临床上，DIAF 在有潜在合并疾病应用多种治疗的患者中可能是严重的[132]。停止使用相关药物通常在几分钟或几小时内复律。当 AF 持续时，其治疗与非 DIAF 患者相似[133,134]。因为药物引起 AF 的机制广泛，DIAF 伴有的组织学变化可能从 EHRAS Ⅰ类-Ⅳ类，差别很大（参照**表 2**）。未来的研究需要评价不同药物对心房组织的特异性效果。

心肌炎

心肌炎是指心脏的炎症性疾病，是暴露于外界（如感染性因素、毒素或药物）或者如自身免疫性疾病等内部触发因素的结果[135,136]。

由于取决于诊断标准，心肌炎发生率很难确定。估测的发病率为 8-10 例/100000 人，是继肥厚型心肌病和冠状动脉性疾病之后导致猝死的的第三大原因[137]。在尸检系列中，心肌炎在猝死年轻人的患病率占 2-42%[138, 139]。活检证实在不能解释的非缺血性扩张型心肌病中，9-16%的患者有炎症浸润[140,141]。

根据“达拉斯标准”，心肌炎定义为存在伴有坏死的心肌炎症浸润和（或）相邻的非缺血心肌细胞变性[142]。根据炎症细胞类型，心肌炎可以被细分为淋巴细胞性、嗜酸性细胞性、多细胞性、巨细胞性心肌炎和心脏结节病[136]。

心房颤动是心肌炎常见的临床表现。在 245 名临床疑似心肌炎的患者中，AF 发生率大约是 30%[143]。仅累及心房的心肌炎罕有诊断[144-146]。这可能反映了心房肌不是尸检或常规心内膜活检样本的现实。在大部分这类病例中，AF 是临床上的主要表现，这表明干扰到心房传导的结构重构的作用[9,147]。巨细胞性心肌炎是一种独特的心肌炎------可能与自身免疫有关------以弥漫性淋巴细胞、大量多核巨细胞、嗜酸性粒细胞浸润，心肌细胞坏死并最终纤维化为特征。自然过程通常是爆发性的，如不治疗死亡率高。关于巨细胞性心肌炎的孤立心房改变于 1964 年首次报道[148]。此后，英文文献中仅描述了少数病例。与典型形式相比，心房病变的病程似乎更为有利[149]。心房巨细胞性心肌炎可能是一种独特的类型，可能与心房特异性自身抗原有关[150]。在心房心肌炎的患者中可观察到 EHRAS Ⅳi 类改变。当心肌炎持续存在并进入慢性期，其特征可能变为 EHRASⅢ类（见**表 2**）。

伴有遗传性复极化紊乱的心房心肌病

心房静止，是心房心肌病的一种严重形式，伴有 SCN5A 和连接蛋白-40 基因杂合子联合突变[151]。已在 AF 患者中发现了钾通道亚单位（如 KCNQ1、KCNH2、KCND3 和 KCNE5）的功能获得性突变或者 KCN5A 的功能缺失性突变[152]。因此，无论是钾通道功能获得或缺失均能引起 AF，这表明复极需要优化调整，任何一个方面的缺陷均可导致心律失常。最近，尽管发现早期复极或 J 波综合征与 AF 相关，但在中年研究对象中，下壁导联上的早复极不能预测 AF[153]。编码心脏 Kir6.1（KATP）通道的 KCNJ8 基因的功能获得性突变，这与 AF 易感性增加和早复极均相关[154]。在房性心律失常和原发性室性心律失常综合征之间无明确关联，其首次报道是在有明显结构异常的情况中发生的[155]。心房颤动在肥厚型心肌病中相对常见（发生率大约 20%）[156]。在致心律失常性右室心肌病中，相当多的患者（高达 40%）可以表现为 AF[157]。没有明显结构性心脏病的原发性心律失常综合征也与 AF 相关。在 Brugada 综合征中，室上性心动过速和原发性 AF/AFL 均有报道[158,159]。在长 QT 综合征（LQTS）患者中，动作电位延长导致心房颤动，这表明存在“尖端扭转”的心房形式[152]。包括左心房容积增加等的“心肌病”的细微形式发生于大约 12%的 LQTS 患者中[160]。现有的报告大部分与 Na^+通道基因的遗传变异有关[161]。早发孤立性 AF 患者中 LQTS 相关 SCN5A 变异发生率也高[162]。LQT3 小鼠模型由于 EADs 易于发生房性心律失常[163]。也存在一些 CPVT 患者中发生房性心律失常的散在报告[164]。综合以上，AF 和猝死综合征之间的关联似乎反映了心房和心室致心律失常的共同机制。

表 4 报道的诱发心房颤动的药物

药物种类	药物	机制
双磷酸盐类	阿仑膦酸钠，唑来膦酸	
心血管		
正性肌力药物	多巴胺、多巴酚丁胺、多培沙明，阿布他明，依诺昔酮，米力农，左西孟旦	肾上腺素能刺激
血管扩张药物	硝酸异山梨酯，氯沙坦，氟司喹南	低血压可能伴有肾上腺素能反射
胆碱能药物	乙酰胆碱	迷走刺激
利尿剂	噻嗪类	低钾血症
呼吸系统		
拟交感神经药	伪麻黄碱，沙丁胺醇，奥西那林，沙丁胺醇，沙美特罗	肾上腺素能刺激
黄嘌呤类	氨茶碱、茶碱	肾上腺素能刺激
中枢神经系统		肾上腺素能刺激
抗胆碱药物	阿托品	肾上腺素能刺激
抗惊厥药	拉科胺，帕潘立酮	
抗抑郁药	氟西汀，反苯环丙胺、曲唑酮	直接心脏抑制效应，交感刺激
抗偏头痛药	恩丹西酮，舒马曲坦	冠状动脉痉挛
抗精神病药	丁二酸洛沙平，氯氮平，奥氮平	直接心脏抑制效应，交感刺激
胆碱能药物	毒扁豆碱，盐酸多奈哌齐	迷走刺激
多巴胺激动剂	阿扑吗啡	迷走刺激
化疗药物		心脏损伤，冠状动脉痉挛，高血压，氧自由基，线粒体钙转运变化，电解质紊乱，炎症
烷化剂	顺铂，环磷酰胺，异环磷酰胺，马法兰	
蒽环类	多柔比星，米托蒽醌	
抗代谢药	卡培他滨，5-氟尿嘧啶，吉西他滨	
抗微管药	多西他赛，紫杉醇	
酪氨酸激酶抑制剂	西妥昔单抗，索拉菲尼，舒尼替尼	
拓扑异构酶抑制剂	安吖啶，依托泊苷	
单克隆抗体类	阿仑单抗，贝伐单抗，利妥昔单抗、曲妥珠单抗	
细胞因子和免疫调节剂	硫唑嘌呤，γ-干扰素，白细胞介素-2，来那度胺	
生殖泌尿系统		
治疗勃起功能障碍的药物	西地那非，他达拉非，伐地那非	低血压伴有肾上腺素能反射
宫缩抑制剂	β2 受体激动剂（己烷双异丙肾上腺素、特布他林），硫酸镁	
激素		
蛋白同化雄性类固醇		结构改变，自主神经活性变化

衰老

在老年犬中，过早搏动明显减慢传导，这与 APD 延长和复极的空间异质性纤维组织含量加倍有关[165,166]。临床标测研究也证实了相似发现，包括传导异常、不应期延长、心肌电压降低和大量的双电位以及碎裂电图[167,168]。已有描述波阵面传导速度的变化与年龄呈负相关，这或许是这些心房改变的结果[169]。组织学上，纤维化病变是最明显的变化（EHRAS Ⅱ类，见**表 2**）。

高血压

高血压至少占 AF 病例的 1/5。[170]。在高血压患者中，左心房扩大和 P 波改变是 AF 发生的预测因素[171,172]。

在小动物模型中，通过夹闭部分主动脉模拟高血压引起 LA 肥大、纤维化，连接蛋白-43 下调和缓慢/非均一性传导[173]。绵羊出生前暴露于皮质醇引起高血压，导致心房传导异常，波长缩短和 AF 增加[174]。Lau 等利用一肾一夹模型调查短期和长期高血压对心房心肌病发展的影响[175,176]。这一模型更多地从本质上反映了肾素-血管紧张素轴的紊乱。短期高血压逐渐使 LA 扩大，降低 LA 排空分数，延长心房不应期，减慢传导并引起 LA 间质纤维化和炎症细胞浸润[175,176]。在明确高血压和 LV 肥厚的患者，存在整体和区域性传导减慢，伴有沿终末嵴的碎裂电图和双电位，以及低电压区域增加[177]。

重要的是，人群研究显示，即使在高血压前期（收缩压 130-139mmHg）患者中，AF 风险也增加[178]。不正常的心房基质是可逆的，研究证实肾素-血管紧张素-醛固酮系统阻滞剂治疗可改善电和结构参数，减少 AF 负荷[179-181]。在顽固性高血压经肾交感神经消融治疗后血压改善的患者，心房传导整体改善，复杂碎裂电活动减少。组织学上，压力负荷引起心房肌细胞肥厚（EHRAS Ⅰ类）。在引起 LV 肥厚和舒张功能减退的更严重的高血压中，也可发生胶原沉积（EHRAS Ⅱ-Ⅲ类）（见**表 2**）。

肥胖

几项以人群为基础的研究证实了在肥胖和 AF 之间的强关联[182-184]。最近的 meta 分析估测，体重指数每增加一个单位，即增加 3.5-5.3%的 AF 额外风险[185]。

已知左房扩张和功能下降是由于肥胖导致心肌病的结果[186]。在肥胖的绵羊模型中，超过 8 个月的进展性的体重增加伴有心房容积、压力和心包脂肪增加，并有心房基质纤维化、炎症和心肌细胞脂质沉积[187]。并伴随有传导速度降低，传导不均一性增加以及心房颤动的可诱发性增加。随着肥胖持续时间延长，在动物中不仅证实有进展性心房病变而且在与心包脂肪交界区的心房肌细胞中有脂肪细胞浸润[188]。

肥胖患者左心房容积和压力高而应变力低，并且 LA 和 PVs 内不应期短[189]。肥胖者心房病变的详细评估显示，左心房外膜脂肪增加，心房传导速度整体降低，碎裂电位增加，整体电压不变，但低电压区域扩大[190]。在与心外膜脂肪层交界区域观察到低电压区。

心包脂肪容积与 AF 发生率、严重程度以及消融的副作用有关[191,192]。心外膜脂肪过多与心房 3D 结构变化相关，心肌细胞中脂肪细胞浸润，心房纤维化可能有利于不均一传导，促进 AF 发生[193-195]。

在长期肥胖的绵羊模型中，体重下降与全身脂肪、心房扩张及间质纤维化减少有关，并伴有血流动力学、心房连接蛋白-43 表达和传导特性改善，使 AF 易感性降低[196]。在人类，对体重和伴随的危险因子积极治疗有利于心包脂肪容积、心房大小、心肌质量的改善，也有利于电生理和电解剖变化，从而降低 AF 可诱发性和 AF 负荷[197]。此外，病态肥胖个体的体重下降与心外膜脂肪减少有关[198]。肥胖个体的体重降低可使 LV 肥厚复原，左房大小减少以及 AF 负荷/严重性降低[199-201]。组织学上，脂肪浸润（EHRAS Ⅳ类），胶原沉积（EHRAS Ⅲ类）均有发生（见**表 2**）。

糖尿病

糖尿病是 AF 发生和发展的独立危险因素[202]。在大鼠糖尿病模型中，心房组织纤维沉积伴有传导速度下降，且 AF 可诱发性增加[203]。与对照组相比，糖代谢异常患者左心房更大，左心房电压更低，激动时间更长[204]。胰岛素抵抗伴有左心房增大和结构异质性增加[205,206]。

在糖尿病患者的心房中，线粒体功能受损，这导致氧化应激[207]。氧化应激和晚期糖基终末化产物（AGE）-AGE-受体（RAGE）系统激活介导循环组织生长因子以及促炎症反应引起心房间质纤维化上调[207,208]。此外，长期高血糖应激可导致 AGE-RAGE 积累、一氧化氮失活以及内皮功能障碍和心肌炎症[209]。

高血糖和 AGE-RAGE 配体交互作用导致连接蛋白-43 磷酸化减少，可能损伤细胞间偶联[210]。晚期糖基化也与心肌钙调控相关，并因此与收缩性有关[211]。这些发现能解释电生理变化，并且是糖尿病中 AF 易损性的核心机制[212]。

积极治疗糖尿病，充分控制血糖可能预防或延缓 AF 发生，尽管没有治疗糖尿病药物对 AF 作用的直接证据。过氧化物酶体增殖物激活受体γ激动剂具有抗炎、抗氧化和抗纤维化作用，因此在控制血糖之外可以提供额外保护，防止 AF[213]。然而，在将这些试验发现外推到糖尿病心肌病患者时应当谨慎。组织学上，心房肌细胞改变是最初的发现，不伴有明显纤维化（EHRAS Ⅰ类）。疾病晚期表现为纤维化，可能转变为 EHRAS Ⅲ类和 EHRAS Ⅳ类（见**表 2**）。

由于瓣膜病所致的心房心肌病

二尖瓣疾病（MVD）和主动脉瓣狭窄（AS）伴有心房结构重构和 AF 倾向。尽管在发达国家，随年龄增加、高血压和心力衰竭发生，常伴随有继发性心房心肌病，在发展中国家，RHD 占 AF 发生比例的 40%以上[214]。

二尖瓣狭窄

John 等报道[215]，在孤立性 MS、存在正常窦性心律并接受二尖瓣成形术的 24 名患者心房中，有效不应期（ERP）无变化或增加、广泛分布或部位特异性的传导延迟以及心肌细胞丢失和片状电瘢痕表明在 AF 发生前即存在结构改变和相应的电生理结局。这些结构变化的相关因素包括直接的心肌效应（Ashoff 小体的特异性炎症），超微结构变化，心房纤维化，免疫反应细胞因子和基质金属蛋白酶重构（MMP-1 和 MMP 减少）[215-217]。在 21 名孤立性 MS 患者中证实，在接受二尖瓣扩张术后，发生了心房逆重构（LA 压力和容积减少，双心房电压改善；以及 6 个月后 RA 电压进一步增加）[218]。相反，在接受成功 AF 消融的孤立性 AF 患者中，心房重构没有逆转；实际上，基质异常在之后的 6-14 个月仍在进展（电压降低和局部不应期增加）[219]。

心房扩大和纤维化是 AF 的发生和维持的重要决定因素。在 AF 和 MVD 患者中可见Ⅰ型胶原和Ⅲ型胶原增加（后者在培养的暴露于机械张力的成纤维细胞中增加）[220]，但是在孤立性 AF 患者中仅能见到Ⅰ型胶原[221]。细胞偶联和肌细胞分离，组织的各向异性以及不均一性传导被认为是局部折返和心律失常的基质。

二尖瓣返流

Verheule 等[222]发现通过二尖瓣部分撕脱伤制造严重二尖瓣返流（MR）1 个月后，心房组织结构和超微结构发生变化。在 19 条 MR 犬的 10 条中均出现有效不应期均匀增加，且诱发持续性 AF（＞1h）；在这一模型中，心房传导形式或速度并无差异。在扩张的左心房中，注意到存在间质纤维化、慢性炎症和细胞糖蛋白累积，但是没有心肌细胞肥厚、肌溶解和坏死。相反，在外科手术造成慢性 MR 的猪中，以及 MR[223]

患者中却描述了心肌细胞肥厚、去分化和变性以及纤维化[12,224]。

高密度寡核苷酸微阵列，富集分析和差异蛋白质组学的方法被用来确定在严重慢性 MR 猪中见到的心房肌病相关的分子调控机制和生物过程的特征[225]。肾素-血管紧张素系统和过氧化物酶体增殖物激活受体信号途径和基因与凋亡、自噬、氧化应激、细胞生长调节以及碳水化合物代谢差异性调节相关[225]。在 MR 猪中，MLC2V（心肌肥厚标记物和心肌细胞收缩性调节的重要因子）变化最为明显。在孤立性严重 MR 的患者中，已证实在心房肌细胞中膜结合 NADPH 氧化酶活性增加，这与细胞肥厚程度和肌溶解相关。作者认为心房张力诱发的 NADPH 氧化酶活性和细胞内氧化应激有助于凋亡、心房收缩障碍和心房扩张的发生[226]。

MR 的矫治使许多心房重构特征得以逆转，功能异常得到矫正。在术后 43 名接受二尖瓣外科手术（成功修复或置换）的慢性器质性 MR 患者手术后早期（30 天）发现早期 LA 逆重构（LA 平均最大容积减少 45%）以及心房有效排空增加[227]，Dardas 等报道了 6 个月时相似的改善[228]。组织学上，MVD 中 EHRAS Ⅲ类是最主要的发现，组织的组织学表现可以在不同时间和不同个体之间有变化，因此所有的 EHRAS 类别在组织中均可发现（见**图 1**，**表 2**）。

主动脉瓣狭窄

尽管 AS 伴有慢性 AF[229]，但缺少 AS 和心房重构的动物模型。Kim 等[173]研究制作了后负荷增加导致 AS（升主动脉绑扎）的大鼠模型，这样会产生 LVH 但没有系统性高血压、心力衰竭或神经内分泌激活，在其离体灌注心脏中研究了心房电重构。在术后 14-20 周在结扎的心脏中出现明显的 LA 肥厚和纤维化。在 20 周时，起搏诱发 AF 的发生率和持续时间增加，伴有平均矢量传导速度降低以及非均一性传导，连接蛋白-43 表达降低，但没有 ERP 改变。重要的是，在 8 周 LVH 程度最大时并没有出现心房重构[173]。

与对照组相比，AS 患者左心房容积较高，并且在瓣膜成形术后明显降低[230]。在有症状的 AS 患者血浆钠尿肽（ANP）水平高于无症状的 AS 患者[231]，N-ANP 水平能够预测心房重构和 AS 外科手术后晚期（2 个月）AF[232]。

综合以上，这些数据支持以基质为基础的 AF 是瓣膜性心脏病伴有的血流动力学异常和心房重构的结果这一概念。在这一例子中，心房重构是引起结构和超微结构异常以及传导改变（与不应期相对应）的多种生物学进程的结果，这有利于 AF 的发生和维持。组织学上 EHRASⅢ类是最主要的发现，但组织的组织学表现在不同时间和不同个体之间存在变化（见**图 1-3**，**表 2**）。心房病理通常也影响特殊传导系统的组织，如窦房结和 AV 结。然而，这些改变已超出了本专家共识报告的范围，本报告主要集中于心房肌细胞和组织。

心房心肌病对心房颤动和房性心律失常发生的影响

关于 AF 机制的争论已经超过 100 年，但是由于全球范围内 AF 负荷的持续增加[233]，对此的持续研究将促进其治疗和预防的改善。当前，关于 AF 中折返机制的辩论有两个相对的方面。其中之一是对 Gordon Moe 原有观点的推动，即颤动，无论是心房还是心室，是由于多个在整个心房中独立移动的独立电波持续随机化的传播[234,235]。另一个是对以下理论的坚持，即颤动是一些高速旋转的旋涡（转子）持续激动，产生“颤动样传导”的结果[236,237]。在两种机制中，APD/不应期缩短均有利于心律失常维持[13,238,239]。另一个多子波假说的先决条件是应当存在缓慢传导，而不是在有转子的条件下。根据转子理论，通过旋转波阵面的曲率动态地形成缓慢传导，这在旋转的中心最为明显，这里不应期最短，传导速度最慢[240]。人类 AF 中，上述两种机制均仍未能充分确立[241]。

无论 AF 的维持机制如何，AF 导致高频心房激动，并且如果其持续，会导致离子通道重构，进一步缩短 APD 和不应期，提高其稳定性。这种 AF 诱发的心房重构在短期内是可逆的（数分钟，数小时或数天），但是当持续数月或数年时几乎不能逆转。对 AF 诱发重构的详细讨论见第三章。关于这些长期变化是如何利

于 AF 的延续尚未得到充分确定。

最近的研究使用了间歇心房快速起搏诱发持续性 AF 的绵羊模型，在第一次检测到 AF 发作后，AF 激动的主导频率（DF）渐进性自发性增高[240,242]。这些结果表明，不同于心动过速诱发的在数分钟或数小时发生的电重构，在 AF 持续数天或数周后，存在继发于 AF 的持续的、进展性的电和结构重构[240,242]。此外，在离体灌流绵羊心脏中，左右心房间 DF 差异与持续性 AF 期间转子的存在、DF 梯度和 LA 后壁激动的向外传播有关[242]，在人类也可见到这一潜在基础[243]。非持续性 AF 的 DF 以一个比率（dDF/dt）逐渐增加，这可以准确预测间断性，非持续性 AF 向持续性、长期持续性 AF 的转变[126]。尽管纤维化逐渐进展[126]，但任何纤维化在转子加速或持续中所起的作用仍然未知。使用不同动物模型的其他研究也证实长期心房快速起搏导致心房纤维化[244]，同时发生的细胞因子释放改变心房电功能[245]。在绵羊模型中，心房结构改变导致 PLA 扩大，可能是转子不太可能与解剖边界碰撞，从而有助于其稳定性和 AF 的持久性[242,246]。

心房心肌细胞显著的张力可能有助于心房心肌病的形成，成为 AF 的致心律失常基质。例如，机械张力是心脏电特性的主要调节因素。由于其“储存容器”的地位和“压力感受器”具有特殊内分泌作用，如分泌钠尿肽的功能，两个心房对机械偶联的变化尤其敏感。许多机械传感器在心房中表达，并有助于膜电特性、机械张力和肌细胞壁变形之间的相互作用[247]。最近，报道了心房肌细胞剪切应力通过刺激连接肌细胞与细胞外基质的整合素调整电压门控钾通道的表面表达[248,249]。在心房血流动力学超负荷时，机械传感器信号途径被激活，这样肌细胞不再能够对剪切应力做出反应。这一过程导致心房复极化加速，增加 AF 易损性[249]。

氧化应激也被认为对 AF 诱发心房重构导致的心肌病以及 AF 延续起重要作用[250]。然而，其活性氧（ROS）介导心房离子重构的方式尚未充分理解。在颤动的心房中，NOX2/4 活性增加，是 AF 中 ROS 的可能来源。线粒体 ROS 可能是另一个重要的氧化应激来源。氧化应激是否直接影响心房 APD 和不应期，从而有利于转子加速和 AF 的稳定性仍有待确定。几个肌浆离子流直接或间接受到 ROS 调节[251]，但是这些机制与人类 AF 的关联仍未被证实。

持续性 AF 激活促炎症细胞因子和心血管疾病及组织损伤相关激素释放，其中包括血管紧张素 II（Ang-II）、肿瘤坏死因子（TNF）-α、白介素（IL）-6 和 IL-8[252]。已证实促炎症因子刺激诸如 NOX 衍生的活性氧、生长因子以及其他激素在 Ang-II 功能中的作用[253]。然而，推定的在 Ang-II 刺激后，活性氧信号靶点的精确分子修饰还未被确定。了解在正常心房 Ang-II 激活 NOXs 可能有助于产生旨在预防与 Ang-II 激活相关 AF 的更好的措施。Ang-II 是众所周知的成纤维细胞激活并分化为肌纤维母细胞的触发因子。促炎症细胞因子也促进离子通道功能障碍，这些与细胞凋亡和细胞外基质重构均使患者易于发生 AF。

最近，心房脂肪组织已成为 AF 病理生理中的潜在参与因素[3,254]。除了旁分泌作用[192]，脂肪组织可以浸润至心房肌细胞心外膜下，并发生纤维化[255]，从而有助于在心外膜层和心内膜束支网络之间电活动的功能分离、传导波中断以及转子形成。孤立性 AF 或快速心房起搏通过对代谢适应性的基因特异性调节促进脂肪生成。因此，可能脂肪组织的浸润和积累反映了继发于心房肌过度工作的代谢应激 191。此外，脂肪组织能诱发纤维化和改变基因表达形式[195,256]。

心房心肌病、系统性生物标记物和心房内血栓形成

心房心肌病和系统生物标记物

心房炎症和炎症的生物标记物

外科损伤或心包炎伴随的中性粒细胞、巨噬细胞和淋巴细胞浸润，促进心房纤维化发生，导致不均一

性和缓慢传导，是折返性心律失常的危险因素[257-261]。这在炎症激活和房性心律失常发生之间提供了机制上的关联。抗炎症干预措施，如强的松对预防无菌性心包炎的中性粒细胞浸润有效，可抑制起搏诱发的心房扑动[262]，在一项具有一定效力，随机化分组的临床试验中发现，类固醇预治疗可减少术后 AF 的发生率[263]。一项关于秋水仙碱效果的研究（NCT001128427）正在进行中。

在持续性高血压的小鼠模型中，Ang-Ⅱ灌注促进心房髓过氧化物酶（MPO，一种中性粒细胞和巨噬细胞氧化生成酶）增加，并促进心房纤维化[261]。在 MPO 敲除小鼠中，对 A-Ⅱ的促纤维化反应被消除。血管紧张素Ⅱ和内皮素-Ⅰ与炎症和促心律失常心房重构相关[2,264-266]。这一证据表明无论在心脏外科手术以及上述情况中，炎症细胞浸润在促进 AF 基质形成中均有重要作用，这是传导不均一性和缓慢传导的结果。

心房颤动中的全身炎症激活

除了血流动力学应激诱发的心房细胞内炎症外，横断面研究证实 AF 伴随有较高的 C 反应蛋白（CRP）水平，这是一种由肝脏产生的，全身炎症反应的敏感但非特异的生物标记物[267]。对心血管健康研究的参与者随访的次级分析进一步揭示了 CRP 升高预测 AF 发生[268]。

随后的研究证实了几种炎症血清学标记物和 AF 之间的关系，包括 IL-6[269]，TNF-α[270]，醛固酮[271]和简单的白细胞计数[272]。在同一研究中的多种炎症标记物分析表明 IL-6 和骨保护素[273]可能尤其重要。在 IL-6 和 AF 之间的关系可能由左心房扩大介导[269]。

虽然炎症标志物预测 AF 发生的证据可被复制[268,27]，但也有大量研究证实房性心律失常似乎有利于炎症：尤其是 AF 转复[275]以及 AF[276]或心房扑动[277]消融可使炎症反应降低。实际上，Marcus 等证实在血液抽出时的心脏节律（AF vs. 窦性）是检测的 CRP 或 IL-6 水平是否增高的重要决定因素[278]。综合以上考虑，这些数据表明在炎症和 AF 之间的关系可能是双向且是进展性的。

心房内采样研究

由于血流状态，尤其是左房耳部起源的血栓栓塞，促进 AF 情况下卒中风险的增加，因此对外周血是否能够充分反映心房内局部可能存在的高凝状态，人们一直保持着兴趣（见**图 10**）[279]。第一个心房内采样研究未能确定在 MS 的持续性 AF 患者中，左右心房样本中的几个高凝标记物与股静脉和动脉血样本之间具有统计学差异[280]。值得注意的是，当与没有 AF 的正常对照组相比时，同样的样本具有统计学差异[279]。相反，随后的研究证实，在 AF 时的冠状窦血液中，血小板急性激活增加，而全身血小板激活（从股静脉中获取）没有相同变化[281]。

为更好地理解炎症和 AF 之间关系，也应用了多部位采样的相似方法。Liuba 等发现在 8 名永久性 AF 患者中，IL-8 在股静脉、右心房和冠状窦中比左、右上肺静脉高（在 10 名阵发性 AF 患者及 10 名对照组中没有这种差异）[280]。

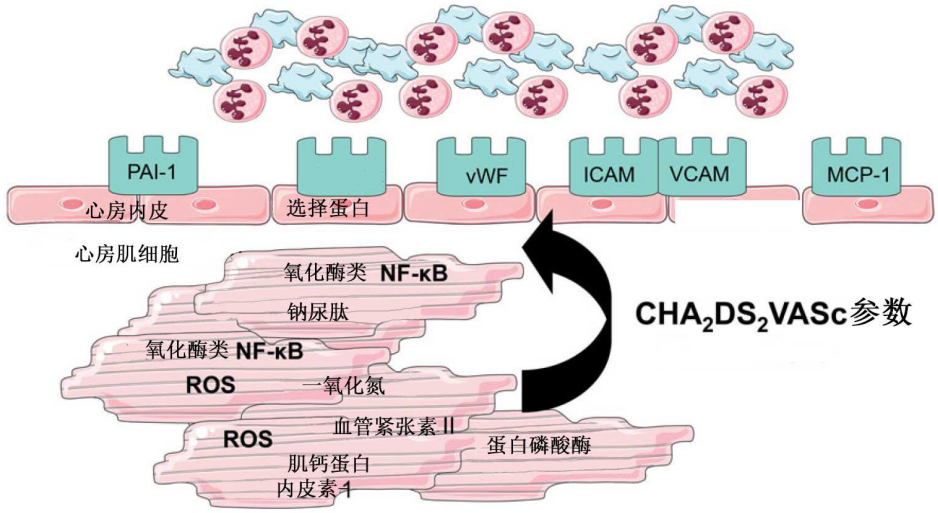

图10：颤动的心房中“心内膜重构”的概念。根据VIRCHOW高凝状态三联征，血流异常、心内膜病变必然共存，在心房内膜中诱发血栓形成。分子研究揭示了左心房组织样本中的重要内膜病变。促血栓形成因子（VWF，粘连分子如VCAM-1，P选择蛋白等；绿色）在内皮细胞表面表达，引起心房内膜血小板和白细胞粘附增加。这启动了心房内膜的血栓形成。几个临床因素如糖尿病、心力衰竭、衰老等（CHA2D2VASC参数）增加肌细胞和内皮细胞内的分子改变（氧化应激途径等），因此，促血栓形成因子表达增加。这些变化并不与体表ECG上无心房颤动直接相关，因此这有助于对为何即使在窦性心律时血栓形成也是增加的进行解释。

实践意义和系统性生物标记物的应用

系统性生物标记物被用于预测 AF 发生和（或）其并发症（**表 5**）。不同的研究测试了炎症指示物、钠尿肽、损伤标记物等在预测 AF，尤其是在外科术后状态中的作用。这些生物标记物中有许多是非特异性的，高水平可能反映感染或脓毒症，急性期反应等[282,283,284]。

CHARGE-AF[包括来自于社区动脉粥样硬化研究（ARIC），心脏健康研究（CHS），Framingham 心脏研究，雷克雅未克年龄、基因/环境易感性研究（AGES）和鹿特丹研究的数据]利用年龄、种族、身高、体重、收缩压和舒张压、近期吸烟、应用抗高血压药物、糖尿病、心肌梗死病史和心力衰竭病史[285]进行预测评分，将 BNP 和 CRP 加入其中，改进了这一统计模型[286]。一旦再次发生，CRP 的加入对模型的改进没有意义。

在另一项评估细胞外基质调节因子（基质金属蛋白酶，MMPs，及其组织抑制剂，TIMPs）和 AF 风险之间关联的研究中，仅仅 MMP9 水平增高与 AF 风险明显相关[287]。具有整合蛋白和金属蛋白酶活性（ADAM）的蛋白酶与心房扩张有关，继而影响心房的力学表现[288]。

除非有明确证据表明对 AF 风险的预测可直接获益，否则与房颤相关的生物标记物的临床获益是值得怀疑的，并且对其进行管理迄今尚未实现。

血栓前期标记物——凝血、血小板

在 150 多年前，Virchow 提出了有利于血栓形成的异常三联征，即：血管壁异常、血流异常和血液成分异常（**图 10**）。在 AF 时，无论是否可通过生物标记物[如 von Willebrand 因子（vWF）、组织纤溶酶原激活物，tPA]、左心房壁免疫组化研究、电子显微镜或功能研究（如血流介导的扩张）识别，血管壁异常与伴有结构性心脏病（如二尖瓣狭窄）和复杂主动脉斑块的血栓栓塞的关联是显而易见的，同时也存在内皮损伤/功能异常[289]。AF 时血流异常在 LA 中超声可见自发血流显影，也可见左心耳部多普勒血流速度减慢。AF 时血液成分异常是显而易见的，从凝血、血小板的异常，纤溶、炎症、细胞外基质的代谢等都直接或间接地与血栓形成，或血栓形成倾向有关。AF 时血小板异常通常是明显的，相对于 AF 本身，它们可能更能反映相关的血管疾病或并发症[290,291]。实际上，与大量富含血小板（“白血栓”）的动脉血栓比较，AF 时的血栓形成主要是富含纤维蛋白（“红血栓”），这为 AF 相关血栓栓塞进行抗凝而不是抗血小板治疗提供了一个机制方面的解释[291,292]。

AF 存在促血栓形成或高凝状态的概念于 1995 年首次提出[293]。无论是在非抗凝或抗凝的个体中，AF 时许多促血栓标记物与随后的卒中和血栓栓塞有关（**图 10**）。最初的研究显示凝血相关因子，如纤维蛋白 D 二聚体（一种纤维蛋白转化和血栓形成的标记物）与卒中风险分层相关，也与血栓栓塞的不良预后有关，无论患者是否接受抗凝治疗[294-297]。相反，血小板标记物没有相关的预后作用[295,298,299]。

血栓形成预测

在 SPAF 研究中，首次显示在非抗凝或次优化抗凝患者中，vWF 能够完善 AF 的危险分层[300]。晚近发现，vWF 既与血栓形成相关，也与 AF 抗凝患者中的出血风险相关[301]。来自于大型 3 期抗凝试验的补充研究报告，D-二聚体、肌钙蛋白、钠尿肽和新型生物标记物（例如 GDF15）水平增加有预后意义[302-304]。这些研究中许多都是在经选择的临床队列研究中进行，危险分层中的预后作用需要在未经选择的包括不同程度卒中风险和不同肾功能的大型“真实世界”队列中进行测试。在 AF 预测中，来自于大型前瞻性非抗凝“真实世界”队列中的生物标记物对卒中危险预测的额外价值的证据是有限的[305]。在病变心房中心内膜血栓形成与氧化应激有关，其有利于血凝块形成，尤其是在左心耳部[306-310]。因此，在 EHRAS 分类的影响及其与心内膜血栓形成病变范围之间关系将在未来的研究中进行评价。有趣的是，AF 的持续时间与观察到的心内膜病变范围无关[309]。

检测心房心肌病和心房心肌病标测和消融中的影像技术

已经确定 LA 扩大伴有不良心血管结局[311-316]。在不存在 MVD 时，LA 大小的增加通常反映了由于 LA 压力增加引起的心房壁张力增加[317-320]以及继发于心房肌病的 LA 功能受损[321,322]。在 LA 扩大和心房颤动以及卒中发生率[323-332]、心肌梗死后的全因死亡率[321,322,333,334]、扩张型心肌病的死亡和住院风险[335-344]以及糖尿病患者主要心脏事件或死亡之间存在明确关联[345]，左心房扩大是舒张功能障碍的严重性和慢性化程度以及 LA 压力增高程度的标志[317-320]。最近的关于 AF 患者多模态成像的共识报告更为详细地总结了心房成像的现状[346]。

表 5 心房颤动中的凝血标记物

研究	AF 组	对照组	AF 中发现的明显异常（凝血标记物增高）*
Gustafsson（1990）507	20（有卒中） 20（无卒中）	40（正常无卒中） 20（有卒中）	D-二聚体，vWF 无论有无卒中病史
Kumagai (1990)508	73	73	D-二聚体
Asakura (1992)509	83	正常	PF1+2，TATIII复合物
Sohara (1994)510	13（阵发性）	正常	TATIII复合物（D-二聚体没有差异）
Lip (1995)511	87	158	D-二聚体，vWF
Lip (1996)512	51	26（健康人）	D-二聚体
Kahn (1997)513	50（之前无卒中） 25（之前有卒中）	31（之前无卒中） 25（之前有卒中）	无卒中的 AF 者中 vs.对照组的纤维蛋白原（在有卒中组间无差异）
Heppell (1997)514	19 例 LA 内有血栓 90 例 LA 内无血栓	不适用	D-二聚体，vWF，如果 LA 内血栓 TATIII复合物
Shinohara (1998)515	45（非瓣膜性）	不适用	在低 vs.高 LAA 流速患者中的 D-二聚体，TATIII复合物。
Feinberg (SPAF III) (1999)516	1531	不适用	PF1+2 与血栓栓塞无关
Mondillo (2000)517	45	35（健康者）	D-二聚体，vWF，s-血栓调节蛋白
Fukuchi (2001)518	16	27（无 AF 的心脏病者）	LA 组织中的 vWF
Conway (2002)296	1321		卒中高危组的 vWF
Kamath (2002)519	93	50（正常）	D-二聚体
Vene (2003)520	113		有心脏事件 vs.无心脏事件者的 D-二聚体
Nakamura (2003)521	7 个非瓣膜性患者的 LA 耳部组织	4 名非心脏性死亡者	vWF，TF
Conway (2003)297	994	不适用	vWF 与卒中风险无关，vWF 与血管事件独立相关
Kamath (2003)522	31（急性发作）	31（健康者）	急性 AF 中红细胞压积增高
Sakurai (2004)523	28（AFL）	27	如果 LAA 功能受损时的 D 二聚体
Inoue (2004)524	246（非瓣膜性）	111	有危险因素患者中的 D-二聚体，PF1+2（NS）
Kumagai (2004)525	16（死后）		心房扩大患者中的 vWF 和蛋白
Marin (2004)526	24（急性发作） 24（慢性）	24（窦性心律的 CAD 患者） 24（健康者）	D-二聚体，vWF，s-血栓调节蛋白（心脏复律后不再有差异）
Nozawa (2004)527	509	111（健康者）	D-二聚体，PF1+2（NS）
Freestone (2005)528	59	40（健康者）	vWF
Nozawa (2006)295	509（非瓣膜性）		D-二聚体（但不是 PF1+2）预测血栓栓塞事件
Ohara (2007)294	591（非瓣膜性）	129	D-二聚体，PF1+2，血小板 4 因子，β血小板球蛋白； D-二聚体，PF1+2（与存在卒中风险因素相关）

AF：心房颤动；AFL：心房扑动；CAD：冠状动脉疾病；LA：左心房；LAA：左心耳；NS：无显著性；vWF：von Willebrand 因子；PF1+2：凝血酶原片段 1+2；TATIII：凝血酶-抗凝血酶III；TF：组织因子；s-血栓调节蛋白：可溶性血栓调节蛋白；*在 AF 组有显著差异，除非另外标示。

超声心动图

超声心动图是筛查和对患者进行系列随访的首选影像学检查方法，包括对 LA 形态和功能的检查[347]。

为评价心房大小，最广泛的报告是在胸骨旁左室长轴切面采用 M 型或二维延迟增强（DE）测量直线长度[324-339,345,347-349]。但是，由于复杂的心房 3D 特征和心房重构的非均一性特征，这一测量方法通常不能提供 LA 大小的精确数据[350-354]。因此，在评价 LA 大小和重构时，在不同的心脏疾病状态下，LA 容积的测量是更为有力的预后指标[329,331,333-339,345,347-360]。二维超声心动图测定的 LA 容积通常小于计算机体层成像或心脏磁共振成象（CMR）所报告的容积[361-365]。2D 成像测定左心房容积最好的方法是盘状总和算法，因为这几乎不涉及几何学上的假设[366,367]。3-D 超声的出现改善了超声容积测定方法的精确性，且与心脏计算机体层成像[368,369]和磁共振成像[370,371]良好相关。与 2D 评价 LA 容积相比，3DE 也有更好的预后预测能力[372,373]。

多普勒超声心动图测定左心房功能

左心房功能可以通过脉冲波多普勒测定舒张晚期（二尖瓣 A 波）充盈进行评价。大量研究使用这一参数作为评价 LA 功能的指标，但是其受到年龄和负荷状态的影响[317,374-382]。肺静脉心房反流速率也被用于测定 LA 功能[317,377,379-382]。在存在 LV 顺应下降和充盈压增高时，心房收缩导致明显的血流反向流入 PVs[80,81]。研究也证实多普勒组织成像可作为心房功能评价的精确指标[383,384]。

超声心动图的新技术

二维斑点追踪超声是已被作为一种敏感的指标来检测在解剖改变发生前的早期功能重构[385-400]。

应变（S）和应变率（SR）成像通过评估心肌运动速率中的空间梯度提供心肌形变的数据[385,388]，[392,393,401-405]。这一指标被用于作为 LA 功能重构和纤维化的替代指标[388-393]。有趣的是，在累及心脏但没有其他超声心动图异常的淀粉样变性的患者中也可观察到伴有应变和应变率变化的 LA 功能障碍[402]。可在不同状态下观察到心房应变的异常，包括 AF、瓣膜病变、心力衰竭、高血压、糖尿病和心肌病[388，389,396-400]。以人群为基础的研究已经证实了 LA 应变分析对长期结局的预后价值[388,394]。

对于 RA 大小的量化几乎没有可提供的研究和临床结局数据。与 3DE 相比，2D 超声心动图技术也低估了右心房容积[343,406,407]。

心脏计算机体层成像

心脏 CT 可以用于精确评价心房容积。心脏计算机体层成像（CCT）得出的容积数据与 CMR 和 3D 超声心动图得出的数据具有可比性，并且优于 2D 超声心动图[371]。导管消融前的 LA 容积以及存在心腔几何构型的不对称性可预测术后维持窦性心律的可能性[408]。由于 LA 扩大，LA 顶部形态开始变平然后成为拱形，这一进展可能与接受 AF 消融患者中非 PV 基质 AF 的产生相关[409]。

CCT 也用于 AF 消融前的血栓筛查。通过多个组别研究了 CT 的诊断精确性，对 19 项研究，2955 名患者的系统回顾报道的敏感性和特异性分别为 96%和 92%，阳性预测值 41%，阴性预测值 99%[410]。当进行延迟成像时，诊断精确性增加至 99%，特异性增加至 100%。使用 CT 成像排除血栓的优势是在 AF 消融前，CCT 是 AF 消融操作中融合电解剖标测系统常规使用的程序。CCT 也提供关于 PVs 解剖和变异的精确信息，在这方面也与 CMR 良好相关[411]。

心房磁共振成像

最近这些年，CMR 已成为房室腔结构和功能评估的金标准，用于临床和科研。CMR 的缺点是昂贵，且与超声心动图相比，应用的限制更多。最近，钆对比剂增强 CMR 技术用于检测心房纤维化[412]。虽然这些方法仍处于较早阶段，并未被广泛使用，但毋庸置疑，其识别心房结构早期改变的能力提高了我们检测从容积或功能评价无法明确的不同程度重构的能力。除了延迟钆增强（LGE）CMR 检测纤维替代外，注射对比剂后 T1 像[413,414]可用于对弥漫性间质纤维化进行定量。两种技术均与侵入性标测中测量的双极电压相关[412]。然而，这些技术需要特殊的成像后处理程序。虽然这些技术通常用于心室成像，但并未广泛用于心房成像，因为在薄壁的心房中实现充分的影像分辨率存在技术挑战[415]。

使用系统化评分系统评价延迟增强范围，最近推出的多中心研究显示 LGE CMR 检测的纤维化范围与 AF 消融结局相关[416]。从纤维化Ⅰ期（＜10%心房壁）到纤维化Ⅳ期（≥30%心房壁），AF 复发风险由 15%增加至 69%。作者建议 CMR 量化的纤维化可能在选择最有可能从 AF 消融中获益的适宜患者上起到作用。延迟钆增强 CMR 也被用于预测窦房结功能障碍的发展[417]、卒中风险[418]以及从阵发性进展到持续性进程的心房颤动[419]。然而，各种研究均着重提出，在将 LGE CMR 作为临床常规工具之前，需要进一步完善准确识别纤维化替代的方法，提高数据分析的可重复性[420,421]。

近年来，大量的研究已经使用 CMR DE 延迟钆增强（LGE）以用非侵入方式确定 AF 消融后瘢痕的范围和分布[422-424]。一些研究观察到，3 个月时，疤痕范围更广泛的患者（或环 PV 周围更大的疤痕比例）房颤复发率更低[423,425]。另一项研究显示在消融时测量的接触力度和 CMR 测定的瘢痕发生范围相关[426]。其他研究显示 PVs 周围瘢痕与侵入性电解剖标测（EAM）的低电压之间一致[427,428]。通过引入 MR 影像识别消融缝隙可在重复程序中实现 PVs 隔离[427,428]。然而，其他研究发现 CMR 瘢痕间隙和标测的 PV 恢复连接部位之间没有关联。一项在 50 例接受广泛消融或仅口部消融的阵发性房颤患者中的研究发现，CMR 可以正确识别出消融损伤分布，其比例从 28%到 54%，取决于所使用的技术[429]。这些作者认为，心房瘢痕 LGE 显像仍不能充分精确可靠地识别消融损伤或其分布范围。是否 CMR 有足够的分辨率能够检测这类瘢痕所在局灶区域仍未完全确定。值得注意的是，Harrison 等使用动物模型研究 CMR 损伤大小与损伤容积在病理学上的相关性。这一相关性关键取决于用于定义瘢痕的像素强度的定义，在这一定义中，小的病变导致在估测的瘢痕容积上出现大的改变[415]。

电解剖影像

电解剖标测系统已经成为侵入性确定心房心肌病基质特征的标准。使用各种技术，这些系统能够快速描述心房特征，并进行 3D 图像的心房解剖再现。PV 解剖结构变异，包括共同开口或额外的肺静脉，均可被识别。可视化软件允许精确测量心房间距[430]和总体容积，但是静脉直径的评估可能是次优的，这是由于静脉易于失真。同时使用来自于操作前得到的心脏 MRI 或 CT，或是实时造影，或是心内超声的 DICOM 影像，心房的解剖成像可获得增强。

EAM 允许解剖重现心房，也能够通过单极或双极电压数据的几何显示评价心房基质，以及心房表面的其他信号特征。低电压区域，电静止，碎裂电位或双电位明确与潜在心房纤维化、外科补片或瘢痕相关。同样的方法，心房电活动可形成影像，用于评估局部传导速度的变化[431]，这种变化可能具有促心律失常作用并使心房颤动持续化。EAM 在房性心律失常激动标测中的应用将在接下来的消融技术部分进行讨论。

电解剖标测已经用于与窦房结疾病[432]、风湿性 MS[215]、房间隔缺损[218,431]、CHF[433]、阻塞性睡眠呼吸暂停[117]以及衰老[167]等相关的心房心肌病的电解剖基质成像中。它是一种能够加深我们对阵发性和持续性心房颤动患者以及[74,434]曾进行 PV 前庭隔离失败的患者心房基质理解的有力研究工具[435]。

不同于心脏 MR、CT 或超声心动图，EAM 需要侵入性导管操作和标测。然而，尽管最近在 MRI 技术

上的进展可对心房瘢痕成像，但是 EAM 影像仍有很大临床可行性和卓越成像能力，能够定义导致心房颤动的心房基质。最近的关于 AF 患者多模态成像的共识报告是有用的详尽参考[346]。

房性心动过速消融

大量单中心随机化研究和大型多中心观察性注册研究证实在维持窦性心律方面 AF 消融优于药物治疗。然而，晚期复发常见，并且更常伴有伴随结构性心脏病的心房基质的进展[436-446]。

在这种情况下，考虑各种潜在的心房心肌病的类型以及它们如何影响消融结局是重要的。这很及时，因为最近已观察到，当我们认识到诸如睡眠呼吸暂停、肥胖、运动耐力等以前不被怀疑与心房颤动具有因果关系的情况时，孤立性 AF 就不存在了[447]。此外，已有的数据表明治疗这些潜在病因可能改善消融的长期结局[199,200,448,449]。另外 LA 消融程序可能改变心房大小、结构和心房机械功能。因此，导管消融可能会影响持续的病理改变和心房血栓形成[450,451]。

标测研究已证实一系列这类对心房产生原发性或继发性影响的病变的共同电生理终点，其中许多显示与心房重构有关，其特征为传导减慢和提示纤维化的心肌电压降低[117,167,177,433,452,453]。磁共振成像技术试图描述心肌纤维化范围的特征，已证实这是消融后 AF 复发的最强有力的独立预测因素[416,454]。是否 EHRAS 分类对在人类心房中导管消融的选择有价值仍有待确定。

年龄和心房颤动消融

在基础和临床研究中均显示年龄增长与心房纤维化增加有关[167,455]。有大量研究评估了老年患者（定义不同，从＞65 岁至＞80 岁）的消融结局[444,445,456-462]。观察性研究一致报告了在随访至 12 个月时，多个操作在老年患者中的成功率高达 80%。但存在相互矛盾的结果，在一项比较性研究中证实，超过 65 岁的老年患者成功率降低，而另一项研究显示在超过 80 岁的患者中成功率与年轻患者队列相似[461,463]。

高血压

高血压是众所周知的另一项心房颤动发生危险因素。标测研究证实与对照组相比，高血压组患者中存在更多的心房病理基质[177,464]。很多单因素分析研究显示高血压是 AF 消融后 AF 复发的危险因素，但是尚不清楚这是否与心房大小一样是独立危险因素。最近开始的研究表明对高血压的积极治疗可改善消融后结局[200,464,465]。

心力衰竭和心房颤动消融

在基础和临床研究中均发现，收缩功能障碍同样伴随心房重构进展以及心房颤动倾向[113,433]。大量研究评估了存在收缩功能明显受损的阵发性和持续性心房颤动患者中导管消融的效果[437,466-473]。虽然常需要重复消融，且随访期通常不超过 12 个月，但主要的证据表明在 50-80%的患者中可成功实现窦性心律。在大多数研究中，成功消融使射血分数明显改善，心房大小减少[470,474]。

代谢综合征和肥胖

许多研究评估了代谢综合征对心房颤动患者消融结局的影响[475-480]。尽管数据有混杂，但是主要的研究和系统性回顾[477]却表明 AF 复发风险高。在 ARREST AF 研究中，BMI 超过 27 以上接受 AF 消融的患者，如果体重能够减少并维持，则复发风险降低[200]。观察性研究证实与未治疗的 OSA 患者相比，经治疗的患者 AF 复发风险较低[481]。

糖尿病对消融结局的影响

几项研究记录到在糖尿病患者中消融后心房颤动复发率增加[204,475,482]。不正常的心房基质和非 PV 触发灶可能是不良结局的基础。

心肌炎的作用

CRP 和 IL-6 等炎症标记物与 AF 风险相关[267,483-48]5。最近表明仅累及心房的巨细胞性心肌炎导致伴有心房扩大的心房颤动[149]。表面上为孤立性心房颤动的患者常被证实有与心肌炎一致的组织学发现[486]；并且那些过去有心肌炎的患者可能存在心房电活动瘢痕、传导异常或心房静止[146,487-489]。基线 CRP 水平与导管消融后的 AF 复发风险相关[278]。最近，秋水仙碱被用于预防 PV 隔离后心房颤动复发[490]。这也可能是由于 AF 本身可导致炎症以及“心房心肌炎”的发生[491]。

心房颤动持续时间对心房心肌病和消融结局的影响

在 AF 患者中进行的纵向研究证实随着时间推移，AF 临床进展在很大程度上与诸如年龄增长、结构性心脏病和高血压等产生的风险相关[492]。一项关于慢性 AF 导致结构变化的近期研究显示，随 AF 负荷增加，心房重构可在一段时间内显著进展，这段时间甚至可短至 1 年。

大量研究已经证实消融后心房大小，偶尔也包括机械功能可能会获得改善[493]，但是至少一项侵入性研究显示在成功消融后 6 个月，心房电生理未获改善[219]。绝大多数评估持续性心房颤动消融后长期结局的研究证实较低的转复为窦性心律的比例和较高的晚期复发率反映了更多的心房病理基质。

长期心房颤动对电重构和结构重构的影响

众所周知，当存在适当的不均一性 AF 基质时，局灶触发能够引起持续的高频折返 AF 驱动灶，即转子。这些转子产生在空间中碎片状分布的波形，因此引起颤动样传导。当高频心房激动维持至少 24 小时时，离子通道重构改变了电生理基质，促进折返的维持，并增加触发活动，进一步有利于 AF 永久化[494]。心房颤动本身导致重构，引起电生理（电学的）、收缩性、和结构改变[495,496]。尽管 AF 经常可在早期被逆转，但超过一定时间后由于这种重构的发生而更难以消除[238,497]。主频分析指出 AF 患者中机制的演变，随着 AF 持续和重构的进展，PV 起源就很少占主导地位了[498]。资料表明长程持续性 AF 患者中，心房重构增加了 AF 驱动子的数量，并改变了其位置使其离开了 PV/口部区域。

导管消融对心房病理学的影响

几个研究测定了导管消融前后的 LA 大小，证实在 AF 导管消融后 LA 内径减少 10-20%[499,500]。尽管这一内径减少的确切机制未知，但显示这与逆重构相一致。已证实早期为维持窦性心律进行的积极干预（包括有需要时进行 AF 消融），可能有助于防止 AF 的“慢性化”及改善长期结局[501]。一项大规模多中心试验正在对这一设想进行测试[502]。

导管消融成功率对心房心肌病的实际影响仍未阐明。不管怎样，心房病理学很可能影响能量到组织的传输，特定形式的心肌病可能对消融过程产生不同影响。然而，实际影响和不同能源与不同心房病理学之间的相互作用仍需进行研究。

结论

根据这一专家共识中心房心肌病的定义，其对心房功能和心律失常形成有明显影响。EHRAS 分类（EHRAS Ⅰ-Ⅳ类）是第一次尝试将心房病理学特征分为不连续的队列。心房组织中疾病相关的组织学变化通常特征不明确，不是特异性的，且随时间变化而改变，因此分类具有挑战性。需要进一步研究完善和验证 EHRAS 分类，并评价其指导临床对 AF 理解和治疗中的价值。不管怎样，更为严谨、精确的心房病理分类可能有助于实现 AF 治疗的个体化目标，这将能够改善其治疗效果。

增补资料

增补资料由 Eruopace 在线提供。

利益冲突：财务关联的详细声明作为增补资料在线提供。

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