

甲状腺功能亢进与心血管疾病关系的研究进展

陈智礼, 李 钊*

重庆医科大学附属第二医院内分泌与代谢病科, 重庆

收稿日期: 2025年12月27日; 录用日期: 2026年1月21日; 发布日期: 2026年2月2日

摘 要

甲状腺功能亢进症(甲亢)是临床最常见的内分泌疾病之一, 其特征为循环中甲状腺激素水平异常升高。由于心脏是甲状腺激素的重要靶器官, 甲亢患者常并发多种心血管疾病, 如心房颤动、心力衰竭及肺动脉高压等, 严重影响患者的生活质量甚至危及生命。因此深入探讨甲状腺激素对心脏的作用机制, 以及甲亢引发心血管疾病的发生机制、治疗策略与预后, 对于提高患者的临床管理水平具有重要意义。文章主要就甲亢和心血管疾病之间的关系进行综述。

关键词

甲状腺功能亢进症, 甲状腺激素, 心血管疾病

Research Progress on the Relationship between Hyperthyroidism and Cardiovascular Disease

Zhili Chen, Ke Li*

Department of Endocrinology and Metabolism, The Second Affiliated Hospital of Chongqing Medical University, Chongqing

Received: December 27, 2025; accepted: January 21, 2026; published: February 2, 2026

Abstract

Hyperthyroidism is one of the most common endocrine disorders in clinical practice, characterized by abnormally elevated circulating thyroid hormone levels. Since the heart is a major target organ of thyroid hormones, patients with hyperthyroidism frequently develop various cardiovascular complications, such as atrial fibrillation, heart failure, and pulmonary hypertension, which markedly impair

*通讯作者。

文章引用: 陈智礼, 李钊. 甲状腺功能亢进与心血管疾病关系的研究进展[J]. 临床医学进展, 2026, 16(2): 419-427.
DOI: 10.12677/acm.2026.162409

quality of life and may even be life-threatening. Therefore, elucidating the mechanisms by which thyroid hormones act on the heart, as well as the pathogenesis, therapeutic strategies, and prognosis of hyperthyroidism-related cardiovascular diseases, is of great importance for improving clinical management. This review summarizes current knowledge regarding the relationship between hyperthyroidism and cardiovascular disease.

Keywords

Hyperthyroidism, Thyroid Hormones, Cardiovascular Disease

Copyright © 2026 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

甲状腺激素作用于几乎所有有核细胞,对机体能量代谢及生长发育具有关键调控作用[1]。甲状腺功能亢进症是指甲状腺自主、持续性过量合成和分泌甲状腺激素所致的一组临床综合征。过量的甲状腺激素可通过多种直接和间接途径影响心血管系统,表现为心率增快、心肌收缩力增强、心脏收缩与舒张功能改变及全身血管阻力降低,从而导致心输出量显著增加。若甲亢长期未得到有效控制,后期可进一步诱发恶性心律失常、充血性心力衰竭、扩张型心肌病,甚至心源性猝死[2]-[4]。2024 年一项涵盖 540,939 名受试者的大型回顾性大数据研究显示,甲亢与多项心血管危险因素升高相关,同时可使心血管疾病总体发生风险增加约 23% [5]。因此,系统阐明甲状腺激素对心脏的作用机制及甲亢相关心血管疾病的发生、发展、治疗和预后,对于提高甲亢患者的精准化临床管理具有重要意义。本文将围绕上述内容进行综述。

2. 甲状腺激素对心血管系统的影响机制

甲状腺主要产生和释放甲状腺激素(TH),包括四碘甲状腺原氨酸(T₄)和三碘甲状腺原氨酸(T₃)。研究表明,TH 主要通过“延迟”基因组效应与“快速”非基因组效应直接影响心脏状态[6]。

2.1. 基因组效应

TH 的基因组效应通过与属于核受体超家族的甲状腺激素受体(THR)相互作用而实现,THR 有两种主要亚型,即甲状腺激素受体 α (THR α)和甲状腺激素受体 β (THR β),这两种亚型都在心血管系统内的心肌细胞中高度表达[7]-[9]。T₃ 与心肌细胞 THR 结合后,与其他核受体如维甲类 X 受体(RXR)二聚化,形成的 TR-RXR 复合物通过与上游启动子区的甲状腺激素反应元件(TRE)结合为同二聚体或异二聚体并招募其他转录辅因子来调节靶基因的表达[10] [11]。受 T₃ 影响的甲状腺特异性基因有很多,这些基因进一步正向或负向调控心脏相关蛋白的表达[12]。在心肌细胞中, α -MHC 和 β -MHC 是两种主要的肌球蛋白重链,它们是心肌细胞收缩装置的重要组成部分,T₃ 能够分别通过上调 α -MHC 基因的表达、下调 β -MHC 基因的表达来增强心肌细胞的收缩能力[13]。近期 Forini 等人[14]利用了体内和体外动物模型展开研究,表明 T₃ 可以作为 Mhrt/Brg1 轴调节剂来影响 MHC 亚型的组成。此外,心脏收缩能力还受肌质网钙泵(SERCA 2)和磷脂结合蛋白(PLB)的调节。SERCA 2 在肌丝收缩的松弛期将钙螯合回肌浆网,而磷酸化的 PLB 会抑制 SERCA 2 将钙送回肌浆网[13] [15]。T₃ 通过诱导肌浆网中 SERCA2 水平升高和 PLB 水平降低,促进心脏舒张期钙的再摄取[16] [17]。因此,我们可以知道 T₃ 对维持心脏的舒张功能至关重要。此外,TH

能够增强心脏 β_1 肾上腺素能受体(β_1 -AR)基因的表达从而使心脏收缩增强以及心率升高[18][19],但是目前 β -肾上腺素能受体系统在 TH 介导的心脏电生理改变是有争议的, 还需要更多的研究进一步讨论[20]。其他还有受 TH 正向调控的钠-钾 ATP 酶、鸟嘌呤核苷酸调节蛋白、电压门控钾通道, 以及负向调控的钠钙交换通道、三碘甲状腺素核受体 α_1 、V 和 VI 型腺苷酸环化酶等[8][15][21]。

2.2. 非基因组效应

与 TH 的“延迟”基因组效应相反, TH 的非基因组效应发生更快, 并且不依赖于 THR 而发挥作用[22]。这种效应发生在核外, 主要发生在质膜上, 调节离子转运蛋白的活性[13]。例如, TH 能激活钠、钾和钙离子通道, 从而改变心肌细胞的电生理特性, 并增加对心脏的离子和变时效应[23][24]。此外, 磷脂酰肌醇 3 激酶(Phosphatidylinositol 3-Kinase, PI3K)/蛋白激酶 B (Protein Kinase B, AKT)信号通路在 TH 发挥非基因组效应中至关重要。Kuzman 等人[25]研究表明, 在新生大鼠心肌细胞中, TH 激活 PI3K/AKT 信号通路保护心肌细胞。并且, Hiroi 等[26]、Carrillo-Sepulveda 等[27]的研究表明, TH 激活此信号通路促进心血管内皮细胞一氧化氮的产生, 通过其对血管平滑肌细胞的松弛作用导致全身血管阻力降低, 从而使肾脏灌注减少, 最终引起肾素-血管紧张素-醛固酮系统(Renin Angiotensin Aldosterone System, RAAS)的激活而影响心脏状态[16]。另外, Bergh 等人发现[28], 在缺乏 TH 核受体的 CV-1 细胞上, T4 能结合整联蛋白 $\alpha v \beta 3$ 上的受体, 其被认为是 T4 诱导的细胞内信号级联激活的起始位点。TH 对心血管系统的非基因组效应所涉及的机制仅得到部分阐明, 也需要研究者们进一步深入探索。

3. 甲状腺功能亢进与心血管疾病

3.1. 心房颤动

众所周知, 甲亢与心房颤动之间存在显著的相关性, 临床甲亢与亚临床甲亢是心房颤动的独立危险因素[29]。Frost 等人[30]进行的一项基于 40,628 名丹麦甲亢患者的大型研究中, 8.3%的甲亢患者会在诊断为甲亢前后 30 天内出现心房颤动或心房扑动。近期, 来自英国一项大型回顾性研究表明, 4189 名 Graves 病患者中有 5.7%在长期随访期间发生心房颤动[31]。而国内 Wong 等人[32]的一项回顾性研究表明, 在 1918 名甲亢患者中, 133 (6.9%)名患者存在心房颤动。因此, 对所有心房颤动患者常规筛查甲状腺功能十分重要。

当心脏正常的窦性机制被抑制或被心房内弥漫性和混乱的电活动模式所取代时, 就会发生心房颤动[33]。Hu 等人[34]在甲亢小鼠心肌细胞上进行了实验, 结果发现甲亢会影响钾离子通道从而导致左右心房肌细胞动作电位持续时间均缩短, 进而诱导房性心律失常的出现。此外, 研究表明, 甲状腺激素改变肺静脉心肌细胞的电生理活动, 甲亢会增加肺静脉致心律失常的可能性从而诱导心房颤动的发生[35]。Stavros 等人[36]研究表明, 在 Graves 病患者中, 活化 β_1 -肾上腺素能自身抗体(AA β_1 AR)和活化 M2 毒蕈碱受体自身抗体(AAM2R)的存在能促进自主神经诱导的肺静脉快速触发放电, 从而促进心房颤动的发生。并且, 甲状腺功能遗传预测因子与心房颤动同样密切相关, 比如说 TSH 水平的遗传介导变异会调节心房颤动风险[37]、遗传性 FT 3: FT 4 比值升高和甲亢与心房颤动增加相关[38], 这也可以得出, 亚临床甲亢与心房颤动的发生同样相关。

甲亢相关性心房颤动的管理在于控制心率、节律以及避免卒中等严重并发症的发生[18]。抗甲状腺药物与控制心率药物(如 β 受体阻滞剂、洋地黄和地尔硫卓)联合使用是常用治疗方案[39]。而关于节律的控制, 在甲亢相关性房颤的治疗中处于次要地位, 多用于持续性或难治性房颤以及血流动力学不稳定的情况, 因为在甲亢得到控制后, 往往会自动地从房颤心律转为窦性心律[40]-[42]。关于甲亢相关性房颤与非甲亢相关性房颤患者出现卒中风险的差异, 目前并未达成共识。Siu 等人[43]所发表的一项前瞻性研究显示, 与

非甲亢相关性房颤患者相比, 甲亢相关性房颤患者缺血性卒中事件的发生率更高。近期一项韩国全国性队列研究同样支持此观点[44]。相反, 近期 Lin 等人[45]所发表的一项大型队列研究结果显示, 甲亢相关性房颤患者缺血性卒中和全身性血栓栓塞的发生率均低于非甲亢相关性房颤患者, 并且与是否接受抗凝剂无关。2022 年 Liu 等人[46]所发表的一项回顾性研究显示, 在 CHA₂DS₂-VASc 评分较低的情况下, 口服抗凝药的甲亢相关性房颤患者与未口服抗凝药的甲亢相关性房颤相比, 出现缺血性脑血管疾病或大出血事件的风险差异无统计学意义。目前 2020 年欧洲心脏病学会以及 2023 年美国心脏病学会发表的指南认为, 甲亢相关性房颤患者管理原则应与一般房颤患者相同, 通过评估 CHA₂DS₂-VASc 评分决定是否抗凝治疗[40] [47]。但是, 甲亢相关心房颤动中, CHA₂DS₂-VASc 评分未将甲亢这一可导致高凝状态、心房结构与血流动力学异常的关键因素纳入评估, 可能低估部分患者的真实血栓风险; 并且甲亢相关心房颤动多为短暂或可逆性, 随甲状腺功能恢复可转复窦律, 其栓塞风险与典型慢性非瓣膜性房颤不同, 而 CHA₂DS₂-VASc 无法反映房颤持续时间及甲状腺功能控制情况。因而, 在甲亢房颤患者中, 单纯依赖 CHA₂DS₂-VASc 评分指导抗凝可能导致风险评估不足或治疗过度, 抗凝决策应结合甲状腺功能状态、房颤持续性、心房结构与功能评估以及出血风险, 采取更加个体化的策略。

3.2. 心力衰竭

心力衰竭是约 6% 的甲状腺功能亢进患者的首发临床表现, 其中约 50% 存在左心室收缩功能障碍[48]。此外, 甲亢患者也常常观察到有左心室舒张功能障碍[49]。如前所述, TH 能够增强心脏 MHC α 、 β 1-AR 基因的表达从而导致儿茶酚胺释放增多, 以及 TH 能激活肾素血管紧张素醛固酮系统[18] [21]。同时, H 能够增强心脏 SERCA 2 表达增加, 以及 PLB 的表达减少[13]-[16]。所以我们可以推测, 在甲亢患者中, 循环中过量的 TH 可以通过影响这些因子的表达或活性而参与心力衰竭的发生。一方面, MHC α 、 β 1-AR 基因表达的增强以及 RAAS 系统的激活, 会导致耗氧量、液体潴留和血容量增加, 还会导致心率和心输出量增加, 引起高输出量性心力衰竭, 长此以往, 心肌储备能力下降, 心肌收缩能力也会下降。另一方面, 通过影响 SERCA 2 和 PLB 表达的平衡, 从而影响心肌细胞钙再摄取, 也会导致心脏舒张功能障碍。

目前关于纠正甲亢引起心衰的措施国内外指南并未特殊说明, 故认为治疗原则与一般心衰人群相同。虽然甲亢引起的心力衰竭常为高输出量性心力衰竭, 但随着病情的进展, 也会引起低输出量性心力衰竭, 需谨慎选择抗心衰药物。同样, 快速纠正甲亢也至关重要, Mitchell 等人[50]研究报道, 在 2225 名心力衰竭患者中, 与甲状腺功能正常患者相比, 甲亢状态与死亡相对风险增加 85% 显著相关。另外一项前瞻性研究中, 甲亢新发心衰患者甲状腺功能正常恢复后, 心力衰竭症状有所改善, 但在长期随访期间, 多达 33% 的左心室收缩功能障碍患者患有持续性扩张型心肌病[48]。因此对于甲亢相关性心衰患者, 长期随访评估患者的心功能十分重要, 以期尽早干预和改善这类患者的预后。

3.3. 肺动脉高压

根据 2022 年欧洲心脏病学会/欧洲呼吸学会肺动脉高压指南, 肺动脉高压(PAH)是指海平面、静息状态下, 经右心导管检查(RHC)测定的肺动脉平均压(mPAP) ≥ 20 mmHg, 并且建议所有 PAH 患者应检查甲状腺功能[51]。先前有研究表明, 在包含 Graves 病和结节性甲状腺肿的 114 名甲亢患者中, 43% 的人群被诊断为轻度 PAH, 而在健康对照组中未发现 PAH 患者[52]。近期两项研究表明, 甲亢患者 PAH 患病率分别为 35.2% 和 47% [53] [54]。并且, Marvisi 等人[52]、Siu 等人[54]、Hegazi 等人[55]的研究表明, 甲亢合并 PAH 患者在达到甲状腺功能正常状态后 PAH 均消退, 这可能提示甲亢是 PAH 发生的直接原因[56]。

甲亢与 PAH 两者之间的潜在机制尚未明确, 目前主要提出了甲状腺自身免疫假说以及 TH 对肺血管内皮细胞直接作用假说。首先, Sugiura 等人[57]发现, TRAb 诱导免疫介导的肺血管内皮细胞损伤可能在

Graves 病相关的肺动脉收缩压升高中发挥作用。近期 Song 等人[53]发表的一项回顾性研究也表明, 甲亢患者的肺动脉收缩压和 TRAb 水平之间存在显著的正相关性, 但校正年龄、性别等混杂因素后, 这种关系消失了。其次, 研究发现, 伴随甲状腺功能亢进状态的显著血流动力学应激可促进肺血管内皮切应力增加, 通过激活机械敏感性通道来增强胞质内钙浓度的增加, 导致肺血管收缩[58]。此外, Huesseini 等人[59]研究表明, TH 促进肺动脉高压状态下内皮细胞的增殖, 但是甲状腺疾病与 PAH 在肺血管重塑发生发展中的因果关系有待确定。还有其他机制, 例如 TH 还能促进内源性肺血管舒张物质的代谢, 以及抑制肺血管收缩物质的代谢[52]。因此, 甲亢与 PAH 之间的潜在机制需进一步探究。

Qian 等人[60]所发表的一篇前瞻性研究发现, 与甲状腺功能正常的患者相比, 患有甲亢的特发性肺动脉高压(IPAH)患者表现出更好的血流动力学特征和长期生存率, 这可能与甲亢相关性 PAH 患者和甲状腺功能正常的 IPAH 患者之间产生 PAH 的不同病理生理机制有关, 但仍需进一步研究。此外, Song 等人[53]的研究团队还进一步得出血清 FT4 水平升高可能是甲亢患者发生 PAH 的显著独立危险因素。并且, 研究表明, 甲亢患者所表现出来的 PAH 在纠正甲状腺功能后可以得到改善甚至逆转[61]。因此, 我们可以知道, 纠正甲状腺功能亢进对甲亢相关性 PAH 的治疗至关重要。

3.4. 房室传导阻滞

甲亢与房室传导阻滞两者之间的联系目前讨论较少, 甲亢背景下房室传导阻滞的患病率计算尚缺乏。但是也有相关案例报道发现, 在没有其他潜在病因的情况下, 甲亢患者中会发生房室传导阻滞[62]-[64]。并且 Eom [65]所发表的一篇案例报告提示, 房室传导阻滞可作为 Graves 病的首发症状。但需要注意的是, 甲亢状态下发生房室传导阻滞的患者比例很小, 因此两者之间潜在机制目前尚未明确, 需进一步探索。此外, 近期 Ata 等人[66]发表了一篇系统评价, 调查了 87 名在甲亢背景下发生房室传导阻滞患者的临床病程及结局, 他们发现完全性房室传导阻滞是最常见类型, 并且与一度和二度房室传导阻滞相比, 临床结局无显著差异, 以及大多数患者可以单独使用抗甲状腺治疗进行治疗, 起搏器治疗是否会改变临床结局也需进一步研究。

4. 亚临床甲亢与心血管疾病

亚临床甲状腺功能亢进定义为 FT3、FT4 水平正常, 而 TSH 水平降低, 其与心血管疾病的发生也存在联系。研究表明, 亚临床甲亢也是心房颤动的独立危险因素[29]。Nanchen 等人发现, 在亚临床甲状腺功能亢进老年人群中, 发生心力衰竭的风险较甲状腺功能正常的老年人高[67]。另外, 丹麦一项大型回顾性研究结果表明, 相比于非甲亢人群, 临床甲亢与亚临床甲亢患者的全因死亡率均有所增加, 而心力衰竭是这类患者心血管死亡率增加的主要原因[68]。因此, 亚临床甲状腺功能亢进对心律失常、心力衰竭及死亡风险的潜在不良影响不容忽视, 但相关研究较少, 还需进一步探究。

5. 总结

综上所述, 甲状腺激素在心血管系统中发挥着至关重要的作用, 而在甲状腺功能亢进背景下也易诱发心血管疾病。因此, 对于存在心房颤动、心力衰竭、肺动脉高压的患者, 筛查甲状腺功能至关重要。同时在面对甲亢人群时, 需尽早向患者阐明可能发生的心血管事件风险, 密切监测心血管系统的变化, 尽快纠正甲状腺功能亢进状态, 积极预防心血管事件的发生。

参考文献

- [1] Taylor, P.N., Albrecht, D., Scholz, A., Gutierrez-Buey, G., Lazarus, J.H., Dayan, C.M., et al. (2018) Global Epidemiology of Hyperthyroidism and Hypothyroidism. *Nature Reviews Endocrinology*, **14**, 301-316.

- <https://doi.org/10.1038/nrendo.2018.18>
- [2] 中华医学会内分泌学分会, 中国医师协会内分泌代谢科医师分会, 中华医学会核医学分会, 等. 中国甲状腺功能亢进症和其他原因所致甲状腺毒症诊治指南[J]. 国际内分泌代谢杂志, 2022, 42(5): 401-450.
- [3] Chaker, L., van den Berg, M.E., Niemeijer, M.N., Franco, O.H., Dehghan, A., Hofman, A., *et al.* (2016) Thyroid Function and Sudden Cardiac Death: A Prospective Population-Based Cohort Study. *Circulation*, **134**, 713-722. <https://doi.org/10.1161/circulationaha.115.020789>
- [4] Osuna, P.M., Udovcic, M. and Sharma, M.D. (2017) Hypothyroidism and the Heart. *Methodist DeBakey Cardiovascular Journal*, **13**, 60-63. <https://doi.org/10.14797/mdcj-13-2-60>
- [5] Iglesias, P., Benavent, M., López, G., Arias, J., Romero, I. and Díez, J.J. (2023) Hyperthyroidism and Cardiovascular Disease: An Association Study Using Big Data Analytics. *Endocrine*, **83**, 405-413. <https://doi.org/10.1007/s12020-023-03482-9>
- [6] Iordanidou, A., Hadzopoulou-Cladaras, M. and Lazou, A. (2010) Non-Genomic Effects of Thyroid Hormone in Adult Cardiac Myocytes: Relevance to Gene Expression and Cell Growth. *Molecular and Cellular Biochemistry*, **340**, 291-300. <https://doi.org/10.1007/s11010-010-0430-9>
- [7] Grais, I.M. and Sowers, J.R. (2014) Thyroid and the Heart. *The American Journal of Medicine*, **127**, 691-698. <https://doi.org/10.1016/j.amjmed.2014.03.009>
- [8] Cini, G., Carpi, A., Mechanick, J., Cini, L., Camici, M., Galetta, F., *et al.* (2009) Thyroid Hormones and the Cardiovascular System: Pathophysiology and Interventions. *Biomedicine & Pharmacotherapy*, **63**, 742-753. <https://doi.org/10.1016/j.biopha.2009.08.003>
- [9] Olanrewaju, O.A., Asghar, R., Makwana, S., Yahya, M., Kumar, N., Khawar, M.H., *et al.* (2024) Thyroid and Its Ripple Effect: Impact on Cardiac Structure, Function, and Outcomes. *Cureus*, **16**, e51574. <https://doi.org/10.7759/cureus.51574>
- [10] Vargas-Uricoechea, H., Bonelo-Perdomo, A. and Sierra-Torres, C.H. (2014) Effects of Thyroid Hormones on the Heart. *Clínica e Investigación en Arteriosclerosis*, **26**, 296-309. <https://doi.org/10.1016/j.arteri.2014.07.003>
- [11] Novodvorsky, P. and Allahabadia, A. (2017) Thyrotoxicosis. *Medicine*, **45**, 510-516. <https://doi.org/10.1016/j.mpmed.2017.05.013>
- [12] Kaasik, A. (1997) Thyroid Hormones Increase the Contractility but Suppress the Effects of B-Adrenergic Agonist by Decreasing Phospholamban Expression in Rat Atria. *Cardiovascular Research*, **35**, 106-112. [https://doi.org/10.1016/s0008-6363\(97\)00069-2](https://doi.org/10.1016/s0008-6363(97)00069-2)
- [13] Razvi, S., Jabbar, A., Pingitore, A., Danzi, S., Biondi, B., Klein, I., *et al.* (2018) Thyroid Hormones and Cardiovascular Function and Diseases. *Journal of the American College of Cardiology*, **71**, 1781-1796. <https://doi.org/10.1016/j.jacc.2018.02.045>
- [14] Forini, F., Nicolini, G., Kusmic, C., D'Aurizio, R., Mercatanti, A., Iervasi, G., *et al.* (2020) T3 Critically Affects the Mhrt/Brg1 Axis to Regulate the Cardiac MHC Switch: Role of an Epigenetic Cross-Talk. *Cells*, **9**, Article No. 2155. <https://doi.org/10.3390/cells9102155>
- [15] Danzi, S. and Klein, I. (2014) Thyroid Disease and the Cardiovascular System. *Endocrinology and Metabolism Clinics of North America*, **43**, 517-528. <https://doi.org/10.1016/j.ecl.2014.02.005>
- [16] Jabbar, A., Pingitore, A., Pearce, S.H.S., Zaman, A., Iervasi, G. and Razvi, S. (2016) Thyroid Hormones and Cardiovascular Disease. *Nature Reviews Cardiology*, **14**, 39-55. <https://doi.org/10.1038/nrcardio.2016.174>
- [17] Kranias, E.G. and Hajjar, R.J. (2012) Modulation of Cardiac Contractility by the Phospholamban/Serca2a Regulator. *Circulation Research*, **110**, 1646-1660. <https://doi.org/10.1161/circresaha.111.259754>
- [18] Ahmad, M., Reddy, S., Barkhane, Z., Elmadi, J., Satish Kumar, L. and Pugalenth, L.S. (2022) Hyperthyroidism and the Risk of Cardiac Arrhythmias: A Narrative Review. *Cureus*, **14**, e24378. <https://doi.org/10.7759/cureus.24378>
- [19] Hoit, B.D., Khoury, S.F., Shao, Y., Gabel, M., Liggett, S.B. and Walsh, R.A. (1997) Effects of Thyroid Hormone on Cardiac B-Adrenergic Responsiveness in Conscious Baboons. *Circulation*, **96**, 592-598. <https://doi.org/10.1161/01.cir.96.2.592>
- [20] Ortega-Carvalho, T.M., Chiamolera, M.I., Pazos-Moura, C.C. and Wondisford, F.E. (2016) Hypothalamus-Pituitary-Thyroid Axis. *Comprehensive Physiology*, **6**, 1387-1428. <https://doi.org/10.1002/j.2040-4603.2016.tb00708.x>
- [21] Yalcin, Y., Carman, D., Shao, Y., Ismail-Beigi, F., Klein, I. and Ojamaa, K. (1999) Regulation of Na/K-ATPase Gene Expression by Thyroid Hormone and Hyperkalemia in the Heart. *Thyroid*, **9**, 53-59. <https://doi.org/10.1089/thy.1999.9.53>
- [22] Giammanco, M., Di Liegro, C.M., Schiera, G. and Di Liegro, I. (2020) Genomic and Non-Genomic Mechanisms of Action of Thyroid Hormones and Their Catabolite 3,5-Diiodo-L-Thyronine in Mammals. *International Journal of Molecular Sciences*, **21**, Article No. 4140. <https://doi.org/10.3390/ijms21114140>

- [23] Klein, I. and Ojamaa, K. (2001) Thyroid Hormone and the Cardiovascular System. *New England Journal of Medicine*, **344**, 501-509. <https://doi.org/10.1056/nejm200102153440707>
- [24] Barreiro Arcos, M.L. (2022) Role of Thyroid Hormones-Induced Oxidative Stress on Cardiovascular Physiology. *Biochimica et Biophysica Acta (BBA)—General Subjects*, **1866**, Article ID: 130239. <https://doi.org/10.1016/j.bbagen.2022.130239>
- [25] Kuzman, J., Gerdes, A., Kobayashi, S. and Liang, Q. (2005) Thyroid Hormone Activates Akt and Prevents Serum Starvation-Induced Cell Death in Neonatal Rat Cardiomyocytes. *Journal of Molecular and Cellular Cardiology*, **39**, 841-844. <https://doi.org/10.1016/j.yjmcc.2005.07.019>
- [26] Hiroi, Y., Kim, H., Ying, H., Furuya, F., Huang, Z., Simoncini, T., *et al.* (2006) Rapid Nongenomic Actions of Thyroid Hormone. *Proceedings of the National Academy of Sciences*, **103**, 14104-14109. <https://doi.org/10.1073/pnas.0601600103>
- [27] Carrillo-Sepulveda, M.A., Ceravolo, G.S., Fortes, Z.B., Carvalho, M.H., Tostes, R.C., Laurindo, F.R., *et al.* (2009) Thyroid Hormone Stimulates NO Production via Activation of the PI3K/Akt Pathway in Vascular Myocytes. *Cardiovascular Research*, **85**, 560-570. <https://doi.org/10.1093/cvr/cvp304>
- [28] Bergh, J.J., Lin, H., Lansing, L., Mohamed, S.N., Davis, F.B., Mousa, S., *et al.* (2005) Integrin $\alpha v \beta 3$ Contains a Cell Surface Receptor Site for Thyroid Hormone That Is Linked to Activation of Mitogen-Activated Protein Kinase and Induction of Angiogenesis. *Endocrinology*, **146**, 2864-2871. <https://doi.org/10.1210/en.2005-0102>
- [29] Heeringa, J., Hoogendoorn, E.H., van der Deure, W.M., Hofman, A., Peeters, R.P., Hop, W.C.J., *et al.* (2008) High-Normal Thyroid Function and Risk of Atrial Fibrillation: The Rotterdam Study. *Archives of Internal Medicine*, **168**, Article No. 2219. <https://doi.org/10.1001/archinte.168.20.2219>
- [30] Frost, L., Vestergaard, P. and Mosekilde, L. (2005) Hyperthyroidism and Risk of Atrial Fibrillation or Flutter—Secondary Publication. A Population-Based Study. *Ugeskrift for Laeger*, **167**, 3305-3307.
- [31] Okosieme, O.E., Taylor, P.N., Evans, C., Thayer, D., Chai, A., Khan, I., *et al.* (2019) Primary Therapy of Graves' Disease and Cardiovascular Morbidity and Mortality: A Linked-Record Cohort Study. *The Lancet Diabetes & Endocrinology*, **7**, 278-287. [https://doi.org/10.1016/s2213-8587\(19\)30059-2](https://doi.org/10.1016/s2213-8587(19)30059-2)
- [32] Wong, C., Tam, H.V., Fok, C.V., Lam, P.E. and Fung, L. (2017) Thyrotoxic Atrial Fibrillation: Factors Associated with Persistence and Risk of Ischemic Stroke. *Journal of Thyroid Research*, **2017**, Article ID: 4259183. <https://doi.org/10.1155/2017/4259183>
- [33] Zimetbaum, P. (2017) Atrial Fibrillation. *Annals of Internal Medicine*, **166**, ITC33-ITC48. <https://doi.org/10.7326/aitc201703070>
- [34] Hu, Y., Jones, S.V.P. and Dillmann, W.H. (2005) Effects of Hyperthyroidism on Delayed Rectifier K⁺ Currents in Left and Right Murine Atria. *American Journal of Physiology—Heart and Circulatory Physiology*, **289**, H1448-H1455. <https://doi.org/10.1152/ajpheart.00828.2004>
- [35] Chen, Y.C., Chen, S.A., Chen, Y.J., Chang, M.S., Chan, P. and Lin, C.I. (2002) Effects of Thyroid Hormone on the Arrhythmogenic Activity of Pulmonary Vein Cardiomyocytes. *Journal of the American College of Cardiology*, **39**, 366-372. [https://doi.org/10.1016/s0735-1097\(01\)01731-4](https://doi.org/10.1016/s0735-1097(01)01731-4)
- [36] Stavrakis, S., Yu, X., Patterson, E., Huang, S., Hamlett, S.R., Chalmers, L., *et al.* (2009) Activating Autoantibodies to the Beta-1 Adrenergic and M2 Muscarinic Receptors Facilitate Atrial Fibrillation in Patients with Graves' Hyperthyroidism. *Journal of the American College of Cardiology*, **54**, 1309-1316. <https://doi.org/10.1016/j.jacc.2009.07.015>
- [37] Salem, J.E., Shoemaker, M.B., Bastarache, L., Shaffer, C.M., Glazer, A.M., Kroncke, B., *et al.* (2019) Association of Thyroid Function Genetic Predictors with Atrial Fibrillation: A Phenome-Wide Association Study and Inverse-Variance Weighted Average Meta-Analysis. *JAMA Cardiology*, **4**, 136-143. <https://doi.org/10.1001/jamacardio.2018.4615>
- [38] Ellervik, C., Roselli, C., Christophersen, I.E., Alonso, A., Pietzner, M., Sitlani, C.M., *et al.* (2019) Assessment of the Relationship between Genetic Determinants of Thyroid Function and Atrial Fibrillation: A Mendelian Randomization Study. *JAMA Cardiology*, **4**, 144-152. <https://doi.org/10.1001/jamacardio.2018.4635>
- [39] Verma, K.P. and Wong, M. (2019) Atrial Fibrillation. *Australian Journal of General Practice*, **48**, 694-699. <https://doi.org/10.31128/ajgp-12-18-4787>
- [40] Hindricks, G., Potpara, T., Dagres, N., Arbelo, E., Bax, J.J., Blomström-Lundqvist, C., *et al.* (2020) 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed with the Special Contribution of the European Heart Rhythm Association (EHRA) of the ESC. *European Heart Journal*, **42**, 373-498. <https://doi.org/10.1093/eurheartj/ehaa612>
- [41] Nakazawa, H.K., Sakurai, K., Hamada, N., Momotani, N. and Ito, K. (1982) Management of Atrial Fibrillation in the Post-Thyrotoxic State. *The American Journal of Medicine*, **72**, 903-906. [https://doi.org/10.1016/0002-9343\(82\)90850-6](https://doi.org/10.1016/0002-9343(82)90850-6)
- [42] Kostopoulos, G. and Effraimidis, G. (2024) Epidemiology, Prognosis, and Challenges in the Management of Hyperthyroidism-

- Related Atrial Fibrillation. *European Thyroid Journal*, **13**, e230254. <https://doi.org/10.1530/etj-23-0254>
- [43] Siu, C., Pong, V., Zhang, X., Chan, Y., Jim, M., Liu, S., *et al.* (2009) Risk of Ischemic Stroke after New-Onset Atrial Fibrillation in Patients with Hyperthyroidism. *Heart Rhythm*, **6**, 169-173. <https://doi.org/10.1016/j.hrthm.2008.10.023>
- [44] Kim, K., Yang, P., Jang, E., Yu, H.T., Kim, T., Uhm, J., *et al.* (2021) Increased Risk of Ischemic Stroke and Systemic Embolism in Hyperthyroidism-Related Atrial Fibrillation: A Nationwide Cohort Study. *American Heart Journal*, **242**, 123-131. <https://doi.org/10.1016/j.ahj.2021.08.018>
- [45] Lin, Y.S., Tsai, H.Y., Lin, C.Y., Wu, V.C., Chen, T.H., Yang, T., *et al.* (2021) Risk of Thromboembolism in Non-Valvular Atrial Fibrillation with or without Clinical Hyperthyroidism. *Global Heart*, **16**, Article No. 45. <https://doi.org/10.5334/gh.871>
- [46] Liu, S.D., Lin, S.J., Ray, C.Y., Lin, F.T., Lin, W.C. and Wang, L.H. (2022) Associations of Warfarin Use with Risks of Ischemic Cerebrovascular Events and Major Bleeding in Patients with Hyperthyroidism-Related Atrial Fibrillation. *Biomedicines*, **10**, Article No. 2670. <https://doi.org/10.3390/biomedicines10112670>
- [47] Joglar, J.A., Chung, M.K., Armbruster, A.L., Benjamin, E.J., Chyou, J.Y., Cronin, E.M., Deswal, A., *et al.* (2024) 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, **149**, e1-e156. <https://doi.org/10.1161/cir.0000000000001193>
- [48] Siu, C.W., Yeung, C.Y., Lau, C.P., Kung, A.W. and Tse, H.F. (2006) Incidence, Clinical Characteristics and Outcome of Congestive Heart Failure as the Initial Presentation in Patients with Primary Hyperthyroidism. *Heart*, **93**, 483-487. <https://doi.org/10.1136/hrt.2006.100628>
- [49] Yue, W.S., Chong, B.H., Zhang, X.H., Liao, S.Y., Jim, M.H., Kung, A.W., *et al.* (2011) Hyperthyroidism-Induced Left Ventricular Diastolic Dysfunction: Implication in Hyperthyroidism-Related Heart Failure. *Clinical Endocrinology*, **74**, 636-643. <https://doi.org/10.1111/j.1365-2265.2011.03981.x>
- [50] Mitchell, J.E., Hellkamp, A.S., Mark, D.B., Anderson, J., Johnson, G.W., Poole, J.E., *et al.* (2013) Thyroid Function in Heart Failure and Impact on Mortality. *JACC: Heart Failure*, **1**, 48-55. <https://doi.org/10.1016/j.jchf.2012.10.004>
- [51] Humbert, M., Kovacs, G., Hoeper, M.M., Badagliacca, R., Berger, R.M.F., Brida, M., *et al.* (2022) 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. *European Respiratory Journal*, **61**, Article ID: 2200879. <https://doi.org/10.1183/13993003.00879-2022>
- [52] Marvisi, M., Zambrelli, P., Brianti, M., Civardi, G., Lampugnani, R. and Delsignore, R. (2006) Pulmonary Hypertension Is Frequent in Hyperthyroidism and Normalizes after Therapy. *European Journal of Internal Medicine*, **17**, 267-271. <https://doi.org/10.1016/j.ejim.2005.11.023>
- [53] Song, X., Yang, K., Chen, G., Duan, W., Yao, D., Li, S., *et al.* (2021) Characteristics and Risk Factors of Pulmonary Hypertension in Patients with Hyperthyroidism. *Endocrine Practice*, **27**, 918-924. <https://doi.org/10.1016/j.eprac.2021.02.011>
- [54] Siu, C., Zhang, X., Yung, C., Kung, A.W.C., Lau, C. and Tse, H. (2007) Hemodynamic Changes in Hyperthyroidism-Related Pulmonary Hypertension: A Prospective Echocardiographic Study. *The Journal of Clinical Endocrinology & Metabolism*, **92**, 1736-1742. <https://doi.org/10.1210/jc.2006-1877>
- [55] Hegazi, M.O., El Sayed, A. and El Ghousein, H. (2008) Pulmonary Hypertension Responding to Hyperthyroidism Treatment. *Respirology*, **13**, 923-925. <https://doi.org/10.1111/j.1440-1843.2008.01353.x>
- [56] Ma, R.C. and Chow, C.C. (2006) Thyrotoxicosis as a Risk Factor for Pulmonary Arterial Hypertension. *Annals of Internal Medicine*, **144**, 222-223. <https://doi.org/10.7326/0003-4819-144-3-200602070-00022>
- [57] Sugiura, T., Yamanaka, S., Takeuchi, H., Morimoto, N., Kamioka, M. and Matsumura, Y. (2014) Autoimmunity and Pulmonary Hypertension in Patients with Graves' Disease. *Heart and Vessels*, **30**, 642-646. <https://doi.org/10.1007/s00380-014-0518-3>
- [58] Song, S., Yamamura, A., Yamamura, H., Ayon, R.J., Smith, K.A., Tang, H., *et al.* (2014) Flow Shear Stress Enhances Intracellular Ca²⁺ Signaling in Pulmonary Artery Smooth Muscle Cells from Patients with Pulmonary Arterial Hypertension. *American Journal of Physiology-Cell Physiology*, **307**, C373-C383. <https://doi.org/10.1152/ajpcell.00115.2014>
- [59] Al Hussein, A., Bagnato, G., Farkas, L., Gomez-Arroyo, J., Farkas, D., Mizuno, S., *et al.* (2012) Thyroid Hormone Is Highly Permissive in Angioproliferative Pulmonary Hypertension in Rats. *European Respiratory Journal*, **41**, 104-114. <https://doi.org/10.1183/09031936.00196511>
- [60] Qian, Y., Quan, R., Chen, X., Zhang, G., Yang, Y., Chen, Y., *et al.* (2023) Clinical Features and Long-Term Survival in Idiopathic Pulmonary Arterial Hypertension with Thyroid Dysfunction: Insights from a National Multicentre Prospective Study. *ERJ Open Research*, **9**, 00495-2023. <https://doi.org/10.1183/23120541.00495-2023>
- [61] Vallabhajosula, S., Radhi, S., Alalawi, R., Raj, R., Nugent, K. and Cevik, C. (2011) Hyperthyroidism and Pulmonary Hypertension: An Important Association. *The American Journal of the Medical Sciences*, **342**, 507-512. <https://doi.org/10.1097/maj.0b013e31821790f4>

-
- [62] Muggia, A.L., Stjernholm, M. and Houle, T. (1970) Complete Heart Block with Thyrotoxic Myocarditis. Report of a Case. *New England Journal of Medicine*, **283**, 1099-1100. <https://doi.org/10.1056/nejm197011122832010>
- [63] Krishnamoorthy, S., Narain, R. and Creamer, J. (2009) Unusual Presentation of Thyrotoxicosis as Complete Heart Block and Renal Failure: A Case Report. *Journal of Medical Case Reports*, **3**, Article No. 9303. <https://doi.org/10.1186/1752-1947-3-9303>
- [64] Al Bannay, R., Husain, A. and Khalaf, S. (2012) Complete Heart Block in Thyrotoxicosis, Is It a Manifestation of Thyroid Storm? A Case Report and Review of the Literature. *Case Reports in Endocrinology*, **2012**, Article ID: 318398. <https://doi.org/10.1155/2012/318398>
- [65] Eom, Y.S. and Oh, P.C. (2020) Graves' Disease Presenting with Complete Atrioventricular Block. *Case Reports in Endocrinology*, **2020**, Article ID: 6656875. <https://doi.org/10.1155/2020/6656875>
- [66] Ata, F., Khan, H.A., Choudry, H., Khan, A.A., Tahir, S., Cerqueira, T.L., *et al.* (2024) A Systematic Review of the Clinical Characteristics and Course of Atrioventricular Blocks in Hyperthyroidism. *Annals of Medicine*, **56**, Article ID: 2365405. <https://doi.org/10.1080/07853890.2024.2365405>
- [67] Nanchen, D., Gussekloo, J., Westendorp, R.G.J., Stott, D.J., Jukema, J.W., Trompet, S., *et al.* (2012) Subclinical Thyroid Dysfunction and the Risk of Heart Failure in Older Persons at High Cardiovascular Risk. *The Journal of Clinical Endocrinology & Metabolism*, **97**, 852-861. <https://doi.org/10.1210/jc.2011-1978>
- [68] Selmer, C., Olesen, J.B., Hansen, M.L., von Kappelgaard, L.M., Madsen, J.C., Hansen, P.R., *et al.* (2014) Subclinical and Overt Thyroid Dysfunction and Risk of All-Cause Mortality and Cardiovascular Events: A Large Population Study. *The Journal of Clinical Endocrinology & Metabolism*, **99**, 2372-2382. <https://doi.org/10.1210/jc.2013-4184>