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原发性醛固酮增多症患者的甲状旁腺激素水平对心血管疾病的影响

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摘　要

心血管疾病目前仍是全球范围内死亡的主要原因。研究发现受继发性甲状旁腺功能亢进症影响的原发性醛固酮增多症患者似乎有更多心血管合并症的趋势。醛固酮与甲状旁腺激素存在相互作用，且两者之间的相互作用与心血管疾病的发生发展有着紧密的联系，可以进一步增加心血管结局的发生及进展。本综述结合目前的研究探讨原发性醛固酮增多症患者的甲状旁腺激素水平对心血管疾病的影响。

关键词

原发性醛固酮增多症，甲状旁腺激素，心血管疾病

The Effect of Parathyroid Hormone Levels on Cardiovascular Disease in Patients with Primary Aldosteronism

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Abstract

Cardiovascular disease (CVD) is still the leading cause of death worldwide. It was found that pa-

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tients with primary aldosteronism (PA) affected by secondary hyperparathyroidism appear to have a trend toward more cardiovascular comorbidities. Aldosterone interacts with parathyroid hormone (PTH) and their interaction is strongly associated with the development of diseases of the cardiovascular system, which can further increase the risk of cardiovascular disease. This review examines the impact of parathyroid hormone levels on cardiovascular disease in patients with primary aldosteronism in the context of current research.

Keywords

Primary Aldosteronism, Parathyroid Hormone, Cardiovascular Disease

1. 引言

迄今为止，心血管疾病的全球发病率及死亡率仍位居榜首。目前有大量研究已经证实在各种不同的人群中，血清甲状旁腺激素的水平与心血管事件的相关性，这些人群包括健康社区人群[1] [2]、慢性肾脏病患者[3]、糖尿病肾病患者[4]、冠状动脉造影患者[5]等等。然而，目前尚没有深入研究探讨并证实继发性高血压－原发性醛固酮增多症患者的甲状旁腺激素水平对心血管结局的影响。因此，本综述将围绕甲状旁腺激素及醛固酮两种激素去阐明原发性醛固酮增多症患者的甲状旁腺激素水平对心血管结局的影响。

2. 原发性醛固酮增多症与心血管疾病

原发性醛固酮增多症(Primary aldosteronism, PA)是因肾上腺皮质自主分泌醛固酮引起的体内钠和钾潴留、血液容量增加、肾素－血管紧张素系统活性受抑制的疾病，其临床特征主要表现为高血压和低血钾[6]。据文献报道，原醛症的患病率在全球范围为 5%至 12%，最常见的原因是肾上腺腺瘤和肾上腺增生[7]，而在难治性高血压中可高达 17%~23% [8]。在中国新确诊的高血压病人中，PA 的发病率至少达到 4% [9]。

目前越来越多的证据提示原发性醛固酮增多症患者发生心血管疾病的风险较高。既往的一项 1688 名非高血压受试者中进行的前瞻性研究显示，基础醛固酮水平每增加四分位数，血压升高的风险增加 16%，高血压风险增加 17%，与醛固酮水平在下 1/4 的患者相比，醛固酮水平在上 1/4 的患者的血压升高风险提高了 1.60 倍，高血压的发生率也提高了 1.61 倍[10]。此外，一项纳入 31 项研究总计 4546 名原发性醛固酮增多症患者及 52,284 名原发性高血压(Essential hypertension, EH)患者的荟萃分析显示，与 EH 组相比，PA 组发生中风、冠心病以及左心室肥厚的风险增加[11]。另外一项荟萃分析也显示，与原发性高血压患者相比，原发性醛固酮增多症患者可增加脑卒中的患病风险 2.58 倍，冠状动脉疾病的患病风险 1.77 倍，心房颤动患病风险 3.52 倍，心力衰竭患病风险 2.05 倍[12]。

醛固酮水平异常升高作为 PA 的特征[13]，被认为是导致 PA 发生 CVD 风险增加的重要原因[14]。研究发现醛固酮可通过多种途径诱导内皮功能障碍，并激活血管平滑肌细胞中的协同通路来增强动脉纤维化和钙化[15] [16]。醛固酮也可以通过刺激人冠状动脉平滑肌细胞释放促炎分并通过多种机制导致冠状动脉动脉粥样硬化，心肌纤维化和肥大以及电生理改变，从而增加心血管疾病和事件的风险[17] [18] [19]。此外，PA 患者心电图几类不同波峰间期增加，也提示醛固酮对心脏传导也有一定影响[20]。人类研究表

明，在没有心衰及急性心肌梗死的冠心病患者中，醛固酮水平与急性缺血事件及死亡率强烈并独立相关[21]。在急性心肌梗死患者中高醛固酮水平与患者的早期及晚期心血管事件的发生率以及死亡率有关[22]。

综上可以发现醛固酮可通过多种直接或间接作用途径促进心血管损伤的发展，最终增加心血管疾病发生的风险。

3. 甲状旁腺激素与心血管疾病

甲状旁腺激素(parathyroid hormone, PTH)，是由甲状旁腺主细胞产生的碱性单链多肽类激素，由84个氨基酸组成。它的主要作用是调控脊椎动物体内钙和磷的代谢，促使血钙水平升高，血磷水平下降。PTH促使血浆钙离子浓度升高，主要影响的器官是骨和肾脏。PTH能够促使骨钙进入血液，从而提高血液中的钙浓度。此外，PTH还能推动远端小管对钙的再吸收，导致尿钙减少，血钙增加。同时，它也能抑制近端小管对磷的再吸收，增加尿磷酸盐的排泄，从而降低血磷含量。另外，PTH在肾脏中的一个关键功能是激活 α-羟化酶，从而将25-羟维生素D3 (25-OH-D3)转化为具有活性的1,25-二羟维生素D3 (1,25-(OH)2-D3)。PTH的分泌主要受到血浆钙离子浓度的影响。当血液中的钙离子浓度增加时，PTH的生成就会受到限制；反之，当血液中的钙离子浓度下降，就会刺激PTH的生成[23]。

甲状旁腺激素不仅在控制钙稳态中发挥重要作用，而且甲状旁腺激素受体也在血管壁和心肌中表达，这表明PTH对心血管系统有直接影响[24]。目前越来越多的研究证实了甲状旁腺激素与心血管疾病之间的关联。既往在健康社区人群的研究中发现较高的甲状旁腺激素与高血压的发展密切[25]。另外一项以社区为基础的无临床心血管疾病的老年人队列中提示过量的甲状旁腺激素水平与心力衰竭相关[26]。一项纳入1245名健康老年人群的研究提示PTH水平与中国老年人群冠状动脉疾病风险独立相关[27]。并且在冠状动脉疾病(CAD)患者中进行的一项前瞻性研究证实较高的血清PTH水平与CAD患者的钙化性主动脉瓣狭窄独立相关[28]。除此之外，也有研究显示较高的血清PTH水平不仅与亚临床血管疾病[29]、内皮功能损伤和主动脉脉压增加[30]相关，还可能与房颤[31]、卒中[32]、心血管死亡率[33]、心源性猝死和全因死亡率的风险增加有相关性[34]。一项纳入12项研究的荟萃分析也表明PTH水平升高会使CVD发生的风险增加[35]。

以上证据均表明PTH与CVD的发生相关，现已知的研究表明，PTH可通过直接或间接的几种途径影响CVD的发生风险。研究发现甲状旁腺激素可通过改变细胞内钙浓度来改变心脏收缩，促进心肌细胞的凋亡[36] [37]。也有研究提出甲状旁腺激素可通过PKC依赖的磷酸二酯酶活性增加细胞环磷酸腺苷(cAMP)浓度，从而通过增加一些心肌肥厚相关基因的表达来促进心肌肥厚的进展[38]。除此之外，为了解释甲状旁腺激素和CVD之间的复杂联系，必须考虑甲状旁腺激素肾素-血管紧张素-醛固酮系统之间的联系。

4. 醛固酮与甲状旁腺激素的相互作用

越来越多的研究发现甲状旁腺激素和醛固酮相互作用可能会导致心血管损伤，代谢和骨骼疾病的风险成比例地增加[39] [40]。既往研究发现与原发性高血压患者相比，原发性醛固酮增多症患者的血清甲状旁腺激素水平较高[41]。另外一项荟萃分析也显示，与无PA的患者相比，PA患者的血清甲状旁腺激素水平较高[42]。反过来有研究发现有PA是PTH升高的危险因素[43]。通常，原发性醛固酮增多症患者的血清醛固酮浓度越高，血清甲状旁激素的浓度就越高[44]。据报道，较高的血浆醛固酮浓度与醛固酮肾素比与甲状旁腺激素水平独立相关[45]。在PA患者中经肾上腺切除术或盐皮质激素受体拮抗剂给药后，血清PTH水平降低[46]。此外PA患者的甲状旁腺切除术不仅能降低血清钙水平，还能降低血浆肾素和醛

固酮水平[47]。这些结果表明醛固酮与甲状旁腺激素之间存在紧密的相互作用。

一项针对 3074 例接受冠脉造影术的患者的研究表明，血浆醛固酮浓度与甲状旁腺激素均与心血管疾病死亡率独立相关，具有潜在的协同作用[48]。除此之外，有文献提到肾素－血管紧张素－醛固酮系统对人类的 PTH 调节有影响，至少在甲状旁腺肿瘤中的 PTH 分泌细胞中有影响，并且该项研究也提示轻度甲状旁腺功能亢进是人 PA 的特征，可通过肾上腺切除术纠正[49]。目前的大多数研究均支持 PTH 和醛固酮之间有相互影响，而且这两种激素的相互作用可能会进一步加剧目标器官的损伤[50] [51] [52] [53]。

目前有几种可能的机制可以解释醛固酮与 PTH 之间的关系。首先，现有相关研究提示甲状旁腺激素可通过直接的途径刺激醛固酮的分泌。1987 年国外的一项研究证实肾上腺是甲状旁腺激素的靶器官，禽类甲状旁腺激素的生理水平一方面刺激了 cAMP 的产生，另一方面刺激了皮质类固醇分泌醛固酮和皮质酮[54]。Mazzocchi 等人的研究发现 PTH 和 PTH-RP 可通过腺苷酸环化酶/PKA 和 PLC/PKC 依赖性信号传导机制刺激醛固酮的分泌[55]。其次，PTH 也可以通过间接的途径对醛固酮的分泌起到一定作用。有研究表明，PTH 能够通过激活肾脏的入球小动脉肌上皮细胞来促进肾素的分泌，但是，当进行甲状旁腺切除手术后，其肾素的活性会有所下降[56]。现有的大多数研究均提示甲状旁腺激素可通过直接或间接的途径刺激醛固酮的分泌或影响醛固酮的合成[57]。然而醛固酮对甲状旁腺激素的作用仍有待确定。

5. 总结

综上所述，目前大量研究支持原发性醛固酮增多症有明显的心血管疾病风险增加的趋势，并且将其归因于醛固酮。然而，原发性醛固酮增多症甲状旁腺激素水平的提高，证实了甲状旁腺激素与醛固酮之间的相互作用。醛固酮与甲状旁腺激素可独立于彼此对心血管系统产生一定的影响，两种激素共同作用可能会进一步加剧心血管疾病发生的进展。因此，更进一步去探索甲状旁腺激素与醛固酮之间的关系以及两者导致心血管风险增加的机制有重要的意义，这很有可能为 PA 患者的心血管预后的干预提供基础。

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