主动脉夹层的性别差异研究进展

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【摘要】主动脉夹层(AD)是一种典型的性别相关性主动脉疾病。了解疾病的性别差异作为实现精准医学的必要和基本步骤,将有助于为患者做出更准确的诊疗决策。目前仍缺乏对 AD 性别差异的全面了解。现从 AD 的流行病学、危险因素和雌激素对 AD 的影响等方面综述 AD 的性别差异,为 AD 的精准医疗提供证据。

【关键词】主动脉夹层;性别差异;流行病学;危险因素;雌激素
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Gender Differences in Aortic Dissection

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【**Abstract**】Aortic dissection (AD) is a typical gender-related aortic disease. Understanding gender differences in diseases as a necessary and basic step to achieve precision medicine will help patients make more accurate diagnosis and treatment decisions. There is still a lack of comprehensive understanding of gender differences in AD. This article reviews the gender differences in AD in terms of epidemiology, risk factors and the effects of estrogens on AD, providing evidence for the precision medicine of AD.

【**Keywords**】Aortic dissection; Gender difference; Epidemiology; Risk factor; Estrogen

随着精准医学的发展,性别差异作为影响心血管疾病(cardiovascular disease, CVD)发生发展的重要因素,正逐渐被广泛认知[1]。作为灾难性的 CVD,主动脉夹层(aortic dissection, AD)在流行病学、危险因素等方面表现出典型的性别差异[2]。然而,雌激素水平被认为是产生这种差异的重要因素[3]。鉴于此,本文拟从 AD 的流行病学、危险因素和雌激素对 AD 的影响等方面综述 AD 的性别差异。

1　AD 流行病学的性别差异

AD 起病急,死亡率高。由于院前死亡率和世界各地不同的尸检率,AD 的报告发病率差异很大[4]。根据现有流行病学研究统计,AD 总体发病率为(2.53~17.60)/10 万[5]。在北欧, Melvinsdottir 等[6]根据 1992—2013 年在冰岛中心医院出院登记、尸检记录和死因登记的数据报告了 A 型和 B 型 AD 的发生率为 2.53/10 万。在亚洲,来自中国的健康保险研究数据表明 AD 估计发病率为 2.8/10 万[7]。尽管如此,AD 患者性别比例在全球呈现总体类似的趋势,即男性比例普遍高于女性(见图 1)。澳大利亚 AD 患者中男性占比为 61.5%[8],加拿大和美国为 56.0%~65.0%[9-10],国际急性主动脉夹层注册机构(International Registry of Acute Aortic Dissection, IRAD)研究为 67.1%[11],在中国患者群体中这一比例可达 3∶1[12]。女性 AD 的发病率较低被认为是雌激素减少血管炎症从而提供血管保护作用导致[13],而这种自然保护作用在更年期会逐渐消失。

IRAD 数据报告表明,60 岁左右为 AD 发病高峰期[14],女性 AD 平均发病年龄较男性晚 7 年[15],女性因症状和体征不典型,诊断往往会被延迟。然而, Liu 等[16]一项基于中国人群的研究显示,在患有 AD 的人群中 76.1%为男性[平均年龄(51.4±11.8)岁],并且年龄没有显著的性别差异。在临床表现方面,诊断 AD 的男性更容易合并卒中、内脏及肾脏灌注不良[17],而女性常合并高血压和慢性阻塞性肺疾病[18]。在入院患者总死亡率中,女性死亡率较男性高[19];在接受急性手术治疗的患者 30 d 死亡率中,女性比例较高,接受 AD 手术的女性结局比男性差[20]。在接受外科手术治疗的男性中,常以更换主动脉根部的 David 手术为特征,并且术中体外循环和主动脉夹闭时间更长。但目前仍缺乏 AD 在血液标

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志物、心电图及其他影像学方面性别差异的相关研究。因此，需进行大规模、多中心研究，以提供更可靠的证据。新的证据将有助于改善男性和女性 AD 的诊断、治疗和结局。

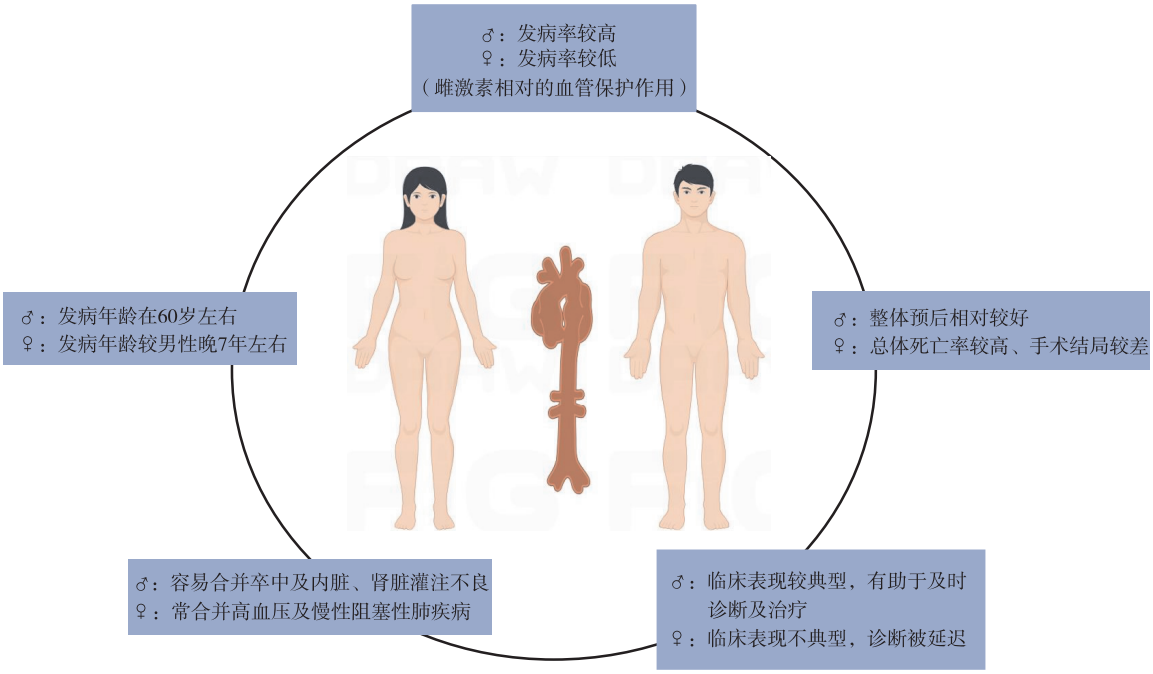

图 1　AD 流行病学的性别差异

2　AD 危险因素的性别差异

高血压与主动脉壁应力相关，是 AD 的重要危险因素。有研究[21-22]报道，在发生 AD 的患者中，高血压患病率为 67.3%～76.6%。据统计，中国高血压人群中男性和女性的患病率分别为 24.5% 和 21.9%[23]；AHA 2017 年更新的报告[24]显示，直到大约 65 岁之后女性高血压患病率变得更高，在年龄≥75 岁人群中男女高血压患病率为 73.4% vs 81.2%。同样，女性雌激素水平在调节血压并导致高血压性别差异中起关键作用[25]。

AD 的危险因素还包括一些先天性遗传性结缔组织病，例如马方综合征、特纳综合征、艾勒斯-当络综合征、勒斯-迪茨综合征、二叶主动脉瓣（bicuspid aortic valve，BAV）等。其中，马方综合征最常见。据研究[26]报道，马方综合征男性患者发生主动脉事件风险高于女性患者。特纳综合征是一种由于全部或部分体细胞中一条 X 染色体完全或部分缺失，或结构发生改变所致的目前最常见的性染色体异常疾病，每 2 500 例活产女孩中就有 1 例[27]，并且 50%的受此病影响的女性与 BAV、主动脉缩窄和/或 A 型 AD 相关。BAV 是最常见的先天性心脏病，男性多见。在一项多中心国际 BAV 患者登记研究[28]中，71.5%为男性，与女性相比，男性更常见孤立性主动脉根部扩张（14.2% vs 6.7%）和弥漫性主动脉扩张（16.2% vs 7.3%）。勒斯-迪茨综合征和艾勒斯-当络综合征患者主动脉表现的性别差异尚未得到研究。

3　雌激素对 AD 的影响

内皮细胞和平滑肌细胞是 AD 发生发展机制中的关键细胞，了解雌激素对血管内皮细胞及平滑肌细胞等的影响，对进一步阐明雌激素对 AD 的作用及潜在机制是必需的。

3.1　内皮细胞

内皮细胞是血管的重要组成部分，在血管稳态中起着关键作用。首先，雌二醇可下调血管内皮细胞中脂多糖或磷脂酰胆碱介导的细胞间黏附分子-1（intercellular adhesion molecule，ICAM-1）和血管细胞黏附分子-1（vascular cell adhesion molecule，VCAM-1）表达以及白细胞介素-1 诱导的 E 选择素、ICAM-1 和 VCAM-1 表达，发挥抗炎作用[29]；其次，雌激素通过与雌激素受体（estrogen receptor，ER）β 结合诱导密封蛋白（claudin）-5 的表达，通过与 ERα 结合诱导 claudin 的表达，从而促进内皮屏障的完整性[30]；再次，雌激素通过促进内皮细胞迁移和增殖来加速内皮愈合[31]。除此之外，有研究[32]表明，ERβ 可通过内皮依赖或非内皮依赖的途径，引起血管舒张，预防血管过度收缩的病理性效应。雌激素可通过增加细胞内的钙离子激活内皮型一氧化氮合酶（endothelial nitric oxide synthase，eNOS），也可通过基因组效应上调 eNOS 的合成，从而促进 NO 的合成，进而引起血管舒张、血压下降[33]。因此，推测雌激素可以通过抗内皮炎症并保持

内皮屏障的完整性进而在 AD 发生发展中起保护作用。

3.2 平滑肌细胞

血管平滑肌细胞和细胞外基质构成的血管壁中间层在维持血管结构和功能方面非常重要。动物实验显示,雄性大鼠主动脉平滑肌细胞生长和迁移明显快于雌性大鼠,是因为雌激素可减弱主动脉平滑肌细胞定向迁移和收缩能力[34];此外,雌激素对主动脉平滑肌细胞具有抗增殖作用[35],通过抑制血管紧张素Ⅱ介导血管平滑肌细胞舒张[36]。Ailawadi 等[37]发现,动脉瘤的形成与基质金属蛋白酶(marix metalloproteinase, MMP)9 的活性降解弹力蛋白有关,雌激素能减少巨噬细胞产生的这种关键性的酶从而抑制动脉瘤的形成。Forbes 等[38]研究发现,雄性腹主动脉瘤(abdominal aortic aneurysm, AAA)比雌性 AAA 有更多的 MMP13,而 MMP13 可导致更多的胶原降解,使得血管壁结构变薄,功能变得更差而导致动脉瘤的形成。AAA 和 AD 均有中膜层退行性改变,其发病机制有着很大程度上的类似,因此可以推测雌激素可能通过下调 MMP 在主动脉的表达,减少细胞外基质降解,从而抑制 AD 的发生发展。

到目前为止,两种最广泛使用的 AD 动物模型是基于皮下注射血管紧张素Ⅱ联合载脂蛋白 E 敲除或 β-氨基丙腈单富马酸盐预处理[39-40]。一项关于建立一种新的小鼠模型,并验证其在人类散发性 AD 形成和性二态性表现方面的应用价值的研究[41]表明,AD 的形成存在显著性别差异,雌激素的补充对 AD 的形成及发生发展起到部分改善及保护作用。目前雌激素对主动脉的炎症、氧化应激、外膜层成纤维细胞的表型转变等在 AD 的形成中起的作用研究甚少。毫无疑问,了解 AD 背后的分子途径和激素机制,可能指导新的治疗方法的发展,以预防和治疗 AD。

4 小结及展望

综上所述,在 AD 的流行病学、临床特征、危险因素及潜在机制等方面存在性别差异。雌激素在高血压等 AD 危险因素性别差异形成中起重要作用,并对 CVD 有一定的保护作用。因此,可以推测雌激素对 AD 可能存在保护作用。本文综述 AD 的性别差异,分析了 AD 性别差异形成的原因,并针对两性治疗方面提出了新的研究方向,呼吁在临床诊疗过程中重视不同性别 AD 患者的临床表现、诊断及治疗,从而改善短期和长期预后。

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