Topol

介入心脏病学

Textbook of Interventional Cardiology

原著 Eric J. Topol
主译 胡大一

第4版

人民卫生出版社

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中文版序

1989年出版的《Topol介入心脏病学》第1版，仅介绍了该领域的“血管成形术（angioplasty）”和“经皮冠状动脉血管重建术（PTCA）”。在之后的15年，介入心脏病学日渐成熟并取得了巨大的发展。现在，该学科涉及的方面包括经皮冠状动脉介入治疗、颈动脉及外周血管的介入治疗、瓣膜成形术、卵圆孔未闭和房间隔缺损的封堵，甚至用于肥厚性心肌病的酒精消融室间隔。

伴随着非手术的介入性心血管技术的发展，出现了全球性的共同努力和广泛合作。介入心脏病学领域的许多突破性进展始于欧洲。1977年，Gruentzig开始使用冠状动脉球囊成形技术；20世纪80年代中期，Sigwart首先使用冠状动脉支架。不同国家的人们不断对介入心脏病学领域进行充实及革新，例如日本的Inoue及其同事创立了目前使用的二尖瓣球囊成形术，巴西Sousa等人的先驱工作使雷帕霉素涂层支架在世界范围内应用。全球人士发展介入心脏病学的共同愿望促进了这一领域技术的快速完善及重大革新的出现。

中国在推动介入心脏病学领域发展中所起的作用特别值得认可。胡大一教授创办的每年一度的“长城国际心脏病大会”是推动介入心脏病学发展的盛会，众多活跃的临床研究者为之做出了重大贡献。我非常尊敬中国的心血管医务界，并且非常期望有机会访问中国这个伟大的国家。

我希望《Topol介入心脏病学》的中文版会成为对中国读者非常有价值的参考书，也期望我们今后在此领域里能够更广泛地合作。

谢谢你们给予的极大支持，也期望继续得到你们的支持。

Eric J. Topol
2004.9.18

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Advance in Percutaneous Techniques for the Treatment of Aortic and Mitral Stenosis

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Introduction of Genetic Material into the Cardiovascular System: Interventional Approaches

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Efficacy of Percutaneous Transluminal Coronary Angioplasty: Randomized Trials of Myocardial Revascularization

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Percutaneous Intervention in Patients with Prior Coronary Bypass Surgery

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Elective Coronary Intervention: Approach, Technique, and Complications

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Stents: The Menu

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Medical Economics in Interventional Cardiology

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Chronic Total Occlusion; Surgical Standby for Percutaneous Transluminal Coronary Angioplasty

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Anticoagulants and Their Use in Acute Coronary Syndromes and Coronary Interventions; Restenosis: The Clinical Issues

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Coated Stents and Local Drug Delivery for the Prevention of Restenosis

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Coronary and Peripheral Angioplasty: Historical Perspective

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Percutaneous Balloon Pericardiotomy for Patients with Pericardial Effusion and Tamponade

目　录

第一篇　药物介入治疗

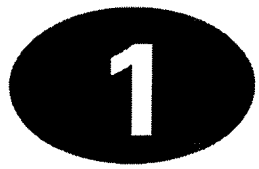
第二篇　冠状动脉和周围血管介入治疗

第三篇 冠脉介入技术的评价

第四篇 瓣膜成形、先天性心脏病和心包疾病

第五篇 介入性心脏病学的成效

第六篇 新 兴 技 术



第一篇

药物介入治疗

第1章

血小板抑制剂在冠状动脉疾病治疗中的作用

Jeffrey Lefkovits, Eric J. Topol

近几十年来人们已认识到血小板在急性冠状动脉综合征中的作用，尤其是近5～10年在对血小板抑制剂作用机制的理解、药物的发展、临床评价以及治疗应用方面均取得了显著进展。抗血栓治疗已不仅仅是控制凝血酶的生成及其活性，控制血小板血栓形成的重要性已引起了人们的重视。在心血管疾病的治疗中，抗血小板治疗所取得的显著效果已明确证实血小板血栓在其疾病发展中所起的中心作用，以及有效控制其发生的必要性。药物的选择也不仅仅是阿司匹林，其他药物诸如噻氯匹定和氯吡格雷，尽管对其作用机制不如阿司匹林了解的透彻，但已经证实了它们对心血管疾病治疗的重要性。有效的静脉药物如糖蛋白（GP）Ⅱb/Ⅲa受体拮抗剂已应用于临床。本章简要讨论血小板在心血管疾病中的作用，以及深入探讨目前临床上应用的抗血小板药物，特别侧重于GP Ⅱb/Ⅲa受体拮抗剂，该类药物已经成为治疗动脉血栓形成的重要药物。

血小板生物学

黏附、激活和聚集

血小板在维持血管完整性方面起着关键性作用[1]。血管损伤后，血小板开始黏附于暴露的血管内皮下成分，主要是胶原[2]。血管性血友病因子（von Willebrand factor，vWF）通过与糖蛋白Ⅰb-Ⅸ-Ⅴ复合物相互作用而迅速黏附在损伤部位[3-5]（表1-1和图1-1）。血小板-血管这种最初的作用启动了包括血小板激活在内的一系列反应。血小板激活后释放颗粒成分，聚集更多的血小板，最终一层血小板覆盖于受损的血管表面，即血小板凝集。凝集的血小板逐渐增多直至出血停止[6]。血小板激活后的其他反应包括血小板颗粒内的糖蛋白，P-选择素移位于血小板表面。这种黏附蛋白属于黏附分子的选择蛋白家族，介导激活的血小板黏附于中性粒细胞、单核细胞以及淋巴细胞亚类[7]。花生四烯酸代谢途径被激活，形成血栓烷A_2。血小板形态发生明显变化，膜磷酸脂蛋白成分重新排列，以提供最有效的膜表面催化凝血过程，特别是激活因子Ⅶ以及形成凝血酶原复合物。虽然激动剂可以激活血小板，但血小板凝集过程主要由血小板膜GP Ⅱb/Ⅲa受体介导[8-10]。该受体主要与纤维蛋白原分子结合，后者在血小板间形成交联桥，将血小板联结在一起以形成血栓的支架。GP Ⅱb/Ⅲa受体除了其在血小板凝集方面的主要作用外，另外一个作用是通过几个可能的配体[11-13]，甚至在血小板未激活的状态下引起血小板黏附[14]。富含血小板的血栓形成是血管损伤后的最初止血反应。在坚固的血小板聚集物形成后，纤维蛋白在血小板间形成交联网，强化血小板聚集物。

基础血小板反应

血小板激活剂引起血小板激活后的一系列反应，包括血小板形态改变、凝集及分泌，伴随细胞内钙离子升高、蛋白磷酸化以及磷酸肌醇途径激活，大部分血小板激活剂的受体由跨胞浆膜的蛋白组成。细胞外及跨膜部分是激活剂结合的主要位点，胞内部分是在受体结合后激活诱导第二信使及离子通道的酶[15-16]。G-蛋白介导受体与效应体之间的反应，激活或抑制该反应[17]。大部分激活剂作用于两种代谢途径以激活血小板。激活磷酸肌醇途径产生第二信使，诸如1、4、5-三磷酸肌醇和二酰甘油，通过增加细胞内钙离子浓度及激活细胞内蛋白激酶而产生激活作用。钙离子也可激活磷酸酯酶A_2，后者可使膜磷脂释放花

生四烯酸，加速血栓烷 A_2 的生成。增加细胞内环磷酸腺苷（cAMP）可产生抑制性作用，前列腺环素、前列腺素 I_2（PGI_2）就是通过抑制环磷酸腺苷而对血小板产生抑制作用。相反，凝血酶、二磷酸腺苷（ADP）和其他血小板激活剂则通过 G_1-蛋白抑制细胞内环磷酸腺苷的生成，主要是抑制腺苷酸环化酶。其他可能机制包括激活环磷酸腺苷磷酸二酯酶，从而加速 cAMP 的代谢[18]。

表 1-1 与血小板黏附、聚集相关的血小板膜糖蛋白受体

受 体	配 体	受体介导的反应	识别序列*
整合素			
$\alpha_2\beta_1$（GP Ⅰa/Ⅱa）	胶原	黏附	DEGA/RGD
$\alpha_5\beta_1$（GP Ⅰc/Ⅱa）	纤连蛋白	黏附	RGD
$\alpha_6\beta_1$	板层素	黏附	不局限于短序列
$\alpha_{\text{Ⅱb}}\beta_3$（GP Ⅱb/Ⅲa）	纤维蛋白原	聚集	KQAGDV/RGD
	纤连蛋白		RGD
	血管性血友病因子		RGD
$\alpha_V\beta_3$	玻基结合素	黏附	RGD
	玻基结合素		RGD
	纤维蛋白原		RGD
	纤连蛋白		RGD
	血管性血友病因子		RGD
非整合素			
GP Ⅰb	血管性血友病因子	黏附	不局限于短序列
	血小板反应素	黏附	CSVTCG
GPⅣ	胶原		?

* 大写字母为氨基酸的单字母编码

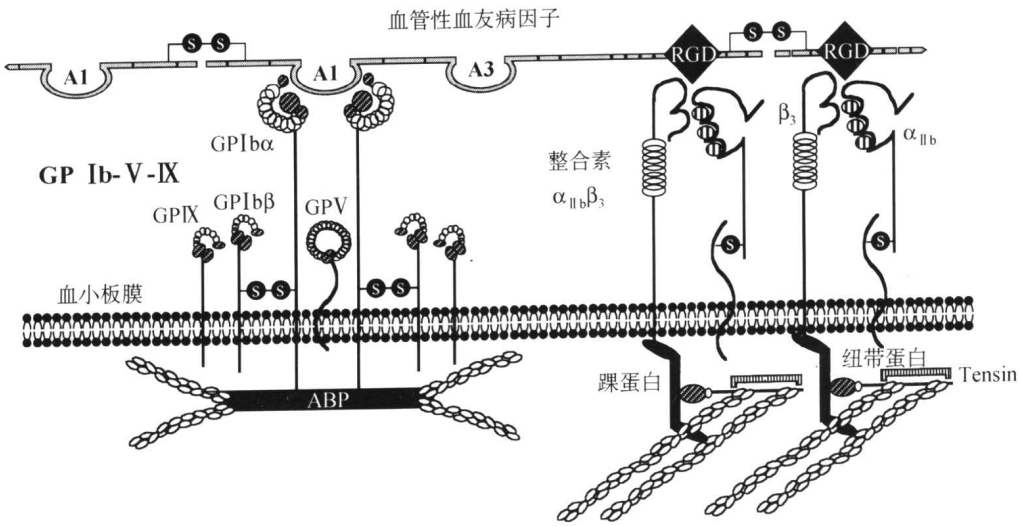


图 1-1 vWF 分子的 A1 区和 A3 区与暴露的内皮下胶原相互作用。A1 区也是血小板膜糖蛋白（GP）Ⅰb-Ⅴ-Ⅸ复合物 GPⅠbα 的结合位点，该复合物是介导血小板黏附的主要受体。vWF 通过精氨酸-甘氨酸-天冬氨酸（RGD）序列与糖蛋白（GP）Ⅱb/Ⅲa 受体识别，并相互作用，在血小板黏附中起次要作用。细胞骨架蛋白，包括肌动蛋白结合蛋白（ABP）、踝蛋白、纽带蛋白和 tensin 蛋白连接膜受体与细胞骨架，在跨膜信号转导与血块凝缩中起作用

血小板糖蛋白受体

血小板膜受体具有多种功能(表 1-1)。大部分糖蛋白介入血小板黏附过程,其中一些属于黏附受体整合素家族。整合素是异源二聚体分子,由 α 和 β 亚基通过非共价键结合在一起。α 和 β 亚基特异性结合形成的受体具有独特配体识别特征(图 1-2)。整合素存在于几乎所有的细胞中,介导各种各样的生理反应[19-21]。糖蛋白Ib 受体(一种非整合素),存在于血小板表面,与糖蛋白Ⅸ和Ⅴ结合在一起,与血管性血友病因子结合,是血小板和血管壁最初连接的主要糖蛋白[3-4]。其他与血小板黏附有关的整合素包括糖蛋白 Ic/Ⅱa($\alpha_5\beta_1$)、纤连蛋白受体、$\alpha_6\beta_1$、板层素受体,以及 $\alpha_V\beta_3$、玻基结合素受体。玻基结合素受体也识别许多同样跟 GP Ⅱb/Ⅲa 受体结合的配体[20]。GP Ⅱb/Ⅲa 受体($\alpha_{IIb}\beta_3$)是目前惟一具有重要临床意义的整合素,已发明了具有抑制其作用的治疗药物。Ⅱb/Ⅲa 是血小板表面最主要的整合素,每个血小板大约有 50000 个 Ⅱb/Ⅲa 受体。Ⅱb/Ⅲa 的识别特异性由两个肽序列决定。精氨酸-甘氨酸-天冬氨酸(RGD)序列,存在于纤维蛋白原和其他黏附配体上,包括纤连蛋白、血管性血友病因子和整合素,与 GP Ⅱb/Ⅲa 受体上的 RGD 结合位点相互作用。另一个与 GP Ⅱb/Ⅲa 结合的主要的肽序列是 KQAGDV,只存在于纤维蛋白原上[22]。

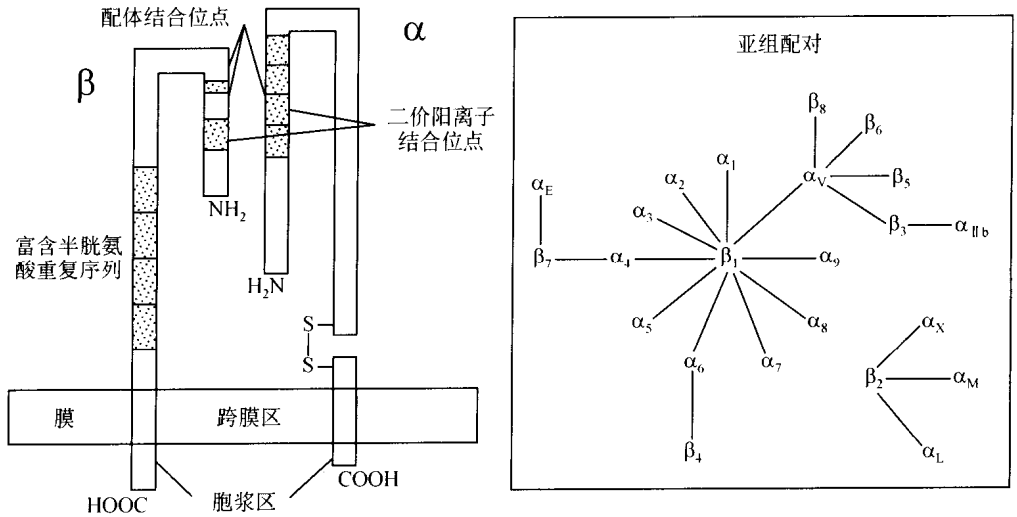


图 1-2　整合素受体的基本结构。整合素家族是由 α 和 β 亚基通过非共价键结合在一起形成的异源二聚体分子。α 和 β 亚基特异性结合形成的受体具有独特配体识别特征。整合素存在于各种细胞中，介导各种各样的生理反应

血小板抑制剂

阿司匹林

迄今为止，已有数百个临床试验证明了阿司匹林在治疗心血管疾病中的无可争议的作用[23-26]。阿司匹林使前列腺素 G/H 合成酶失活，从而引起持续性环氧化酶（COX）活性丧失，这是花生四烯酸转变成血栓烷的第一步[27]。环氧化酶有两种异构体，环氧化酶-1 和环氧化酶-2，阿司匹林相对选择性地作用于环氧化酶-1。受阿司匹林抑制的中间产物，前列腺素 H_2 也是前列腺环素的前体。前列腺环素的作用与血栓烷 A_2 相反，是抑制血小板凝集和扩张血管的。然而，临床上并未发现抑制血栓烷 A_2 合成的阿司匹林剂量可同时抑制前列腺环素的生成[23,28]。阿司匹林主要通过抑制血小板前列腺素合成而起到抗血小板作用，而不是通过所观察到的其他作用，如增强纤溶[29]和抑制凝血[30-31]。血栓烷 A_2 只是 90 多种血小板凝集剂中的一种，因此一般认为阿司匹林是一种弱的血小板拮抗剂。

阿司匹林在胃及小肠上端迅速吸收，消化后约 30～40 分钟血浆浓度达到高峰，肠溶制剂需 3～4 小时方可达到血药浓度高峰。血浆半衰期大约 15～20 分钟。尽管阿司匹林能迅速从血液循环中清除，但一旦作用于血小板，其抑制作用将持续整个血小板的生命周期[32,33]。鉴于每 24 小时的循环中有 10% 的血小板就被更新，所以一次用药大约有 50% 的血小板功能在 5～6 天后方能恢复正常。阿司匹林耐药性，即药效学研究证明未能抑制血小板激活，发生在 8%～26% 阿司匹林服用者中，而且个体对阿司匹林的治疗

试验分类	有资料的试验数	血管事件数 (%) 抗血小板	校正对照	期望值	差异	% 比值下降 (SE)
单用阿司匹林 (mg/d)						
500~1500	34	1621/11215 (14.5%)	1930/11236 (17.2%)	−147.1	707.8	19 (3)
160~325	19	1526/13240 (11.5%)	1963/13273 (14.8%)	−219.9	742.6	26 (3)
75~150	12	366/3370 (10.9%)	517/3406 (15.2%)	−72.0	183.8	32 (6)
<75	3	316/1827 (17.3%)	354/1828 (19.4%)	−18.9	136.5	13 (8)
任何阿司匹林	65	3829/29652 (12.9%)	4764/29743 (16.0%)	−452.3	1717.0	23 (2)

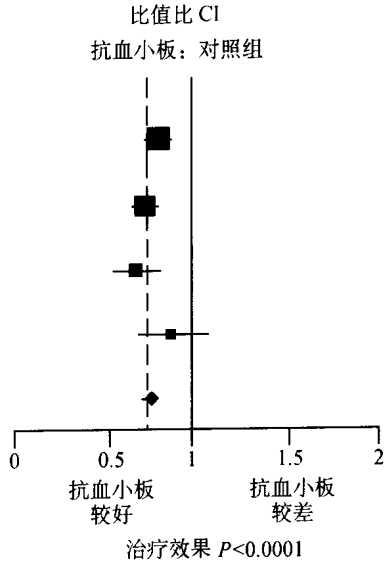


图 1-3 阿司匹林不同剂量对高危患者心血管事件的比较。只对入选的 500 例及以上患者的试验进行集中分析。图中列出了分层比值比和 95% 可信区间

反应也随时间而有较大的差异[34]。

适当的阿司匹林治疗剂量一直是人们争论的问题[23,26]。极小剂量（20～40mg/d）的阿司匹林就能抑制 80% 以上血栓烷 A_2 的生成[35]。临床试验对不同的阿司匹林剂量，30～3900mg/d，进行了比较，除一个试验证明每天 3900mg 的大剂量治疗效果优于每天 975mg[36]，其他试验均未能证实血栓发生率在大剂量和小剂量之间有所不同[23-26,37,38]（图 1-3）。5 个小剂量阿司匹林随机试验（<160mg/d）表明，剂量75～160mg/d 与 160～325mg/d 的效果相同[39-43]。剂量小于 325mg/d 的副作用较少，尤其是胃肠道出血[44-45]。因此，目前推荐的阿司匹林用量为小剂量（75～325mg/d），首次负荷剂量为 325mg。

ADP 受体拮抗剂

噻吩吡啶（thienopyridine）类药仅包括噻氯匹定和氯吡格雷两种，它们在结构和功能上相似。作用机制主要是拮抗血小板 ADP 受体，抑制 ADP 受体激活后的连锁反应[46-48]。它们不影响 COX 途径，但却减弱其他刺激产生的血小板凝集反应，而这些刺激是通过内源性血小板颗粒释放 ADP 起作用的[49]。噻氯匹定和氯吡格雷也可抑制由切变应力引起的血小板凝集[50]，而且对已形成的血小板血栓产生去凝集作用[51]。在整个生命周期中，血小板功能被不可逆地抑制，产生延长的抗血小板作用，通常停药后仍持续 7～10 天。

噻氯匹定体外或静脉滴注的抗凝活性很小，甚至没有抗凝活性，表明它是通过其活性代谢产物起作用[52]。起效时间约需 48～72 小时[46]，主要副作用包括恶心、皮疹以及腹泻，发生率可高达 20%。最严重的副作用是白细胞减少及血栓性血小板减少性紫癜（TTP）[53]。约 2% 的患者出现致命性的白细胞降低，但常为可逆性。血栓性血小板减少性紫癜的发生率很低，约 0.03%，但死亡率却高达 25%～50%[54,55]，因此主张在治疗的前 3 个月内每两周查一次白细胞及血小板计数。

氯吡格雷的作用类似于噻氯匹定，但副作用较少[56,57]。尤其是在随访期内，无骨髓毒性作用是氯吡格雷优于噻氯匹定的主要之处。氯吡格雷和噻氯匹定之间无共同的代谢产物。与噻氯匹定一样，氯吡格雷也是通过代谢产物起作用[47-58]。首次剂量为 300～450mg，可在 6 小时内达到最大血小板抑制作用，维持剂量为 75mg/d[53-61]；而噻氯匹定为每天两次，每次 250mg[58,62,63]。氯吡格雷耐受性好，无阿司匹林的胃肠道副作用[64]，尽管有血栓性血小板减少性紫癜的个案报道[56,66]，但常可逆。一系列调查表明，在用药后 14 天内共发生 11 例血栓性血小板减少性紫癜（美国）[67]，其中一些患者同时服用了其他可引起血栓性血小板减少性紫癜的药物。总之，由氯吡格雷引起的致死性血栓性血小板减少性紫癜的并发症非常罕见，类似于一般人群中的发生率，即每 370 万人中发生 1 例。