

DOI: 10.13210/j.cnki.jhmu.20241230.003

网络出版地址: <https://link.cnki.net/urlid/46.1049.R.20241230.1604.006>

肝硬化患者QT间期研究新进展

李叶¹, 李生浩[✉], 王晴晴[✉], 张露¹

(1. 大理大学公共卫生学院, 云南 大理 671000; 2. 昆明市第三人民医院肝病综合科, 云南 昆明 650000)

[摘要] 诸多研究表明, 肝硬化可能累及心脏导致患者心功能受损和电生理异常, 后者主要表现为QT间期延长, 其与病情的严重程度密切相关, 并可能对肝硬化患者的预后造成不良影响。但肝硬化患者心脏方面的损害病情往往较隐匿, 静息状态下无明显症状, QT间期也不被重视, 导致当患者出现QT间期延长时未能及时识别和干预, 造成患者在应激状态时出现不同程度的心功能损害, 甚至可能危及生命。目前对肝硬化患者QT间期延长的研究较少, 现就肝硬化患者QT间期延长的发生率、机制、影响因素、预后等方面进行阐述, 以期为进一步深入研究防治策略奠定基础。

[关键词] 肝硬化; QT间期; QT间期离散度; 肝硬化心肌病

[中图分类号] R575.2 **[文献标志码]** A **[文章编号]** 2097-5953(2025)08-0634-07

New research progress in QT interval of patients with liver cirrhosis

LI Ye¹, LI Shenghao[✉], WANG Qingqing[✉], ZHANG Lu¹

(1. School of Public Health, Dali University, Dali 671000, China; 2. General Department of Liver Disease, Kunming Third People's Hospital, Kunming, 650000, China)

[Foundation Project]: This study was supported by the Regional Science Foundation Project of the National Natural Science Foundation of China (82260408); Scientific Research Fund Project of Yunnan Provincial Department of Education (2024J0863); and Kunming Science and Technology Bureau Social Development and Science and Technology Benefit to the People Plan Project (2023-1-NS-002)

[Author]: LI Ye, E-mail: 2859167573@qq.com.

[Correspondence to]: LI Shenghao, Associate Chief Physician, E-mail: doctorlee3h@163.com; WANG Qingqing, Associate Chief Physician, E-mail: wangqingqing1511@163.com.

Received: 2024-09-12

Revised: 2024-12-13

JHMu, 2025;31(8):634-640

View from specialist: It is creative, and of certain scientific and educational value.

[Abstract] Many studies have shown that cardiac involvement of cirrhosis may lead to impaired cardiac function and electrophysiological abnormalities in patients, the latter of which is manifested as prolonged QT interval, which is closely related to the severity of the disease and may cause adverse effects on the prognosis of patients with cirrhosis. However, the heart damage in patients with cirrhosis is often insidious, without obvious symptoms in the resting state, and the QT interval is overlooked, leading to the failure to identify and intervene in time when the QT interval extends, resulting in different degrees of cardiac function damage in patients in the stress state, and may even be life-threatening. At present, there are few studies on QT extension in patients with cirrhosis, and the incidence, mechanism, influencing factors and prognosis of QT extension in patients with cirrhosis are expounded, in order to lay a foundation for further research on prevention and treatment strategies.

[Key words] Cirrhosis; QT interval; QT interval dispersion; Cirrhosis cardiomyopathy

肝硬化患者伴门静脉高压会导致内脏动脉舒张, 血管活性物质紊乱^[1], 同时, 交感神经和肾素-血管紧张素-醛固酮系统激活从而形成全身和内脏高

动力循环, 心脏长期保持高心输出量, 因负荷过重最终导致收缩和舒张功能障碍以及电生理异常^[2]。QT间期延长是肝硬化患者中十分常见的电生理现

[基金项目] 国家自然科学基金地区科学基金项目(82260408); 云南省教育厅科学研究基金项目(2024J0863); 昆明市科技局社会发展与科技惠民计划项目(2023-1-NS-002)

[作者简介] 李叶, E-mail: 2859167573@qq.com。

[通讯作者] 李生浩, 副主任医师, E-mail: doctorlee3h@163.com; 王晴晴, 副主任医师, E-mail: wangqingqing1511@163.com。

[收稿日期] 2024-09-12

[修回日期] 2024-12-13

[网络出版时间] 2024-12-31 10:23:52

象^[3,4],是心脏受累的早期标志^[5],甚至有人认为QT间期的变化是肝硬化并发症中的新实体^[6]。随着肝硬化患者接受肝移植及各种治疗机会的增加,人们对心脏相关并发症的认识也不断提高,QT间期延长在临床上也日益受到关注,本文将围绕其研究进展进行简要综述。

1 QT间期定义及肝硬化患者的QTc计算

QT间期是指从心室肌除极开始至复极终止过程所持续的时间,其代表心室收缩的长度。QT间期取决于心率,因此其正确解释需通过心率进行校正表示为校正QT间期(corrected QT interval, QTc),以提高在不同时间和不同心率下QT间期测量的准确性^[7]。

QTc间期通过QT间期(秒)除以R-R间期(秒)的平方根进行计算。Bazett公式是肝硬化患者最常用的校正公式,但有研究发现它过度校正了QT间期,并没有完全消除QT长度与心率之间的关系,该公式在心率高时校正过度,心率低时校正不足,导致QT间期延长的程度在该人群中被高估或低估^[8]。目前认为较可靠的用于研究肝硬化患者QT间期异常的校正法是Fridericia法,以心电图校正QTc>440 ms定义QT间期延长,QTc间期延长表示心脏复极化时间延长^[9]。但也有最新的美国心脏协会建议的QT间期延长标准为:男性QTc>450 ms,女性QTc>470 ms^[10]。

2 肝硬化患者QT间期延长发生率

Day等^[11]首次在酒精性肝硬化中发现QT间期延长。随后多项研究表明,在不同病因的肝硬化患者中均常出现QT间期延长^[12,13],且与病毒性肝炎肝硬化及非酒精性肝硬化患者相比,酒精性肝硬化患者QT间期延长出现更频繁^[9,13,14],但QT间期延长似乎与肝硬化的病因无明确关系^[15]。Bernardi等^[16]的研究首次评估了QT间期延长在肝硬化患者中的发生率,发现47%的患者出现QT间期延长,随着研究的深入,发现其发生率大约为30%~70%^[7,12,17,18]。

3 QT间期延长的可能机制

QT间期延长的机制尚未完全明确,目前提出的肝硬化患者QT间期延长的可能机制归纳起来大致包括以下几点:

3.1 自主神经功能障碍

自主神经系统失衡被视为肝硬化患者的综合性合并症,其可调节心室复极化,常通过心率变异性来评估。Bilous等^[19]发现肝硬化患者心率变异性指数与最大和平均QT及QTc之间存在显著正相

关,且自主神经系统状态特征的评估取决于QT间期,推测其可能是肝病患者QT间期延长的基础。已有研究报道自主神经功能障碍是肝硬化患者QT间期延长的原因之一^[20]。

3.2 血清去甲肾上腺素水平改变

肝硬化患者血清中去甲肾上腺素水平升高可能会影响自主神经功能而影响QT间期。肝硬化患者尤其是伴腹水的患者,有效循环血容量不足,使得肾上腺-交感神经兴奋,循环去甲肾上腺素水平持续升高,导致心脏 β 肾上腺素受体的数量减少、敏感度降低,功能受损,去甲肾上腺素摄取减弱,引起心肌损伤,使心肌细胞信号传导减慢,复极延迟^[21]。

3.3 肝硬化心肌病

有研究表明在心肌病的无症状过程中可使用最大和平均QT及QTc来验证肝硬化性心肌病的诊断,直到出现心肌损伤的第一个临床体征,推测在肝硬化心肌病中观察到的心脏结构异常及肝硬化心肌病形式的潜在心功能障碍会导致QT间期延长^[22]。王爱鱼等^[23]对96例肝硬化患者的尸解病理检查发现,40.6%的患者心肌结构异常,镜下检查可见心肌间质充血水肿或点状出血、心肌断裂、间质性心肌炎,甚至心肌坏死,这表明心肌结构或功能损害可能是影响心肌复极导致QT间期延长的重要因素。相反,Koshy等^[18]对439名接受肝移植检查的患者进行研究表明,QT间期延长与以肝硬化心肌病为特征的结构性或功能性心脏异常无关,并提出肝硬化心肌病和QT间期延长是两个不同的实体,具有不同的病理生理起源的观点。

3.4 心肌细胞膜流动性异常

心肌细胞膜流动性异常影响跨膜离子交换。在多项研究中均表明心肌细胞上一个或多个钾离子通道显著性功能障碍可能是肝硬化患者QT间期延长的原因之一^[16,24]。心肌细胞上钙离子依赖性短暂的钾离子外流通道和延迟的钾离子整流通道两种钾离子通道电导受损,使钾离子通道对 K^+ 通透性降低, K^+ 外流减少,降低了向外复极化的钾电流强度,使心肌细胞膜钾电导降低,引起心脏传导功能异常,心肌细胞信号传导减慢,复极延迟,最终导致患者QT间期延长^[25]。

3.5 门体分流

部分QT间期延长的肝硬化门静脉高压患者在行经颈静脉肝内门体分流术后,降低了门脉压,增强了门体分流,QT间期进一步延长,这些说明门体分流是QT间期延长的原因之一^[26],其机制可能是门体分流导致心脏代偿失调,大量血液从内脏转

移到体循环,中心循环血容量突然增加,导致心输出量和右心压力增加,最终因心脏负荷过重导致收缩和舒张功能障碍,同时中心循环血容量突然增加,进一步促使肝硬化患者产生的类毒素、NO等毒性物质进入循环系统,损伤患者肝功能而影响心脏功能,加重心肌细胞离子通道障碍,心脏传导系统被抑制,影响心肌复极^[27]。

3.6 门静脉高压

QTc延长与门静脉高压有关^[28],门静脉高压通过促进门体分流使来自内脏区的肝脏活性物质(如胆盐和胰岛素)进入体循环中损伤心肌细胞膜和引起自主神经功能障碍,延长心室收缩期、使QRS波群变宽而导致QT间期延长^[26]。

3.7 药物使用及电解质紊乱

QTc间期延长和许多常用药物(吩噻嗪、红霉素、加压素、三环类抗抑郁药)及电解质紊乱(低钾血症、低钙血症、低镁血症)等有关^[7]。药物可能是通过与心脏K离子通道的意外相互作用而阻断了延迟整流钾电流致晚期复极阶段延缓^[29]。低钙血症可能主要通过L型钙通道上的钙依赖性失活机制产生校正QT间期延长。较低的细胞外钙导致钙电流减少,随后导致细胞内钙需要更长的时间才能达到诱导L型钙通道上的钙依赖性失活的临界阈值,由此产生的心室肌细胞复极化时间延长^[30]。

4 QT间期延长相关影响因素

QT间期受生理条件(如年龄和性别)的影响,老年患者和女性QT间期更长^[12,31],男性QT间期延长的患病率远高于女性^[32]。性别对QT间期的影响可能与雌雄激素之间的平衡改变有关,晚期肝硬化常发生性腺激素代谢紊乱,各种病生理条件使得女性心脏复极时间延长,最终导致了QT间期更长,雄激素具有维持心脏电生理稳定的作用,雄激素缺乏可能是男性患者QT间期延长的原因^[33]。

血浆胆汁酸浓度过高及心肌细胞膜中胆固醇含量异常增加会影响心肌细胞膜流动性,从而导致 β -肾上腺素能受体功能异常及心脏肥大和心肌细胞凋亡,严重影响心肌收缩力和电生理活动,从而导致心脏功能障碍和引起QT间期延长^[28]。此外,心输出量、每搏输出量、血管外周阻力、动脉血压等血流动力学指标^[34]和内皮素、白介素等细胞因子^[8]对QT间期也有影响。

5 QT间期延长与肝硬化病情严重程度的关系

Child-Pugh和终末期肝病模型(MELD)评分是最常用来评估肝硬化患者肝脏储备功能的传统模型,它们的评分越高病情越严重^[35]。虽有部分研究

称QT间期与Child-Pugh评分间无相关性,认为QTc间期延长与肝硬化严重程度无关^[9],但仍有研究表明肝硬化患者QTc间期延长与Child-Pugh和MELD评分均密切相关,QTc间期延长患者的Child-Pugh评分更高,且肝功能分级越高,QT间期延长的发生率和QT间期长度较无延长者均明显增加^[3,15,36];QTc间期延长患者的MELD评分较无延长者也更高^[15,36,37]。

当肝硬化患者出现相关并发症时也预示着患者病情加重,同时QT间期延长情况也更加明显。肝硬化腹水患者QTc间期明显长于无腹水的患者^[38],在肝硬化伴食管胃底静脉曲张、肝性脑病中也存在类似现象^[9],急性胃肠道出血可使QTc间期进一步延长^[39]。

6 QT间期延长与肝硬化患者的预后

QT间期延长会影响肝硬化患者的预后^[28,37]。有研究通过QTc间期延长、MELD-Na评分、既往消化道出血和血清白蛋白浓度等参数创建的风险评分系统来分析肝硬化患者的死亡风险,发现随着评分增加,患者生存率逐渐降低,证实QTc间期延长增加了6周死亡风险^[39];同样QTc间期延长是肝硬化腹水患者3年死亡率的独立预测因素^[40];伴有急性胃肠道出血的肝硬化患者往往出现QTc间期延长,这类患者中,死亡组QTc间期延长的发生率及QTc间期的长度均高于存活组^[41]。

但也有研究认为QT间期延长不会影响肝硬化患者的院内死亡率^[31],部分研究也称QTc间期延长与肝硬化腹水患者的1年死亡率无关^[42]。Bal等^[43]对409例肝硬化患者进行了平均八到九年的随访研究发现,QTc间期延长患者的生存率明显低于未延长者,但根据Child-Pugh评分调整后,这种差异便消失了,也提示QTc间期延长并不是死亡率的影响因素。

针对上述争议本课题组需要扩大样本量,设计更为广泛的大型队列研究来探索QT间期延长对肝硬化患者预后的影响,分析其争议的原因。

7 β -受体阻滞对肝硬化患者QT间期的影响

β -受体阻滞剂不但可降低肝硬化患者的门脉压,还可通过调节心脏交感神经和迷走神经的兴奋程度从而改善QT间期延长^[44],这种效应在短效和长效 β -受体阻滞剂中均存在^[45]。QT间期延长的肝硬化患者在予以短效或长效 β -受体阻滞剂后均出现QT间期缩短,不同的是在QT间期正常的患者中,短效 β -受体阻滞剂没有任何影响,而长效 β -受体阻滞剂反而会延长QT间期,且QT间期变化与肝静

脉压力梯度有关的现象只存在于短效 β -受体阻滞剂中^[46,47]。在失代偿期肝硬化或肝硬化合并难治性腹水的患者中,使用 β -受体阻滞剂可能导致心输出量减少和肾损伤,影响患者预后^[48]。但事实上, β -受体阻滞剂常用于预防肝硬化患者胃底静脉曲张破裂出血,且其治疗肝硬化合并食管胃底静脉曲张破裂出血患者的QT间期延长是安全的,使用后患者没有出现任何明显的心动过缓表现^[49]。综上,对于肝硬化并发QT间期延长的患者,短期使用 β -受体阻滞剂有一定积极的治疗价值。

8 肝移植与QT间期

QTc间期延长的肝硬化患者在接受肝移植后QTc间期将会缩短^[50],甚至超过半数患者6个月内就已发生这种现象^[51]。但Ko等^[52]研究却发现,肝移植术后的早期QTc间期其实是延长的,而是在6个月后才出现缩短或逆转。

有研究报道QTc间期延长与患者术中心脏事件发生率无关^[53],且不影响死亡率^[9,53],但也有研究认为QTc延长可能是肝移植围手术期心血管不良事件频发的原因之一^[18,54],其使围手术期心脏骤停和室性心律失常发生风险显著升高并与术后死亡率相关^[55],且死亡率似乎与QTc间期延长时间呈正相关^[50]。

肝移植术后肝硬化患者QT间期将缩短。但QT间期何时发生变化及其与临床结局的关系尚未存在争议,这些问题仍需更大规模的临床试验来解答。

9 QT离散度与肝硬化的关系

QT离散度是QT间期研究中的一个重要指标。QT间期离散度(QT interval dispersion, QTd)为体表12导联心电图上QT间期的最大值与最小值之差,同样经心率校正表示为校正QT间期离散度(corrected QT interval dispersion, QTcd),两者均可反映心室肌复极不同步性或电活动不稳定性, DQT ≤ 60 ms视为正常^[56]。

有研究表明肝硬化患者的QT间期延长似乎与QTd增加无关^[57],在此基础上,有作者认为,在心室壁的另一水平上,可能存在心肌细胞复极延迟,而无复极的空间和时间异质性^[58]。QTd增加可能是由心肌结构变化和与舒张性心肌病相关的自主神经系统改变引起的^[59]。舒张压、 β -受体阻滞剂、血管紧张素转化酶抑制剂或血管紧张素II受体阻滞剂的使用与QTd密切相关^[57],肝移植后QTd显著下降^[60]。QTd增加的患者易发生折返性室速,诱发严重室性心律失常^[61]。Moaref等^[62]研究发现肝硬化

组的QTd显著高于对照组,且与MELD评分相关,其可能是肝硬化患者预后的影响因素和室性心律失常的有效预测因子。在一项研究中作者根据Child-Pugh分级分析QT参数与疾病严重程度之间的潜在关系,发现在肝硬化组中,QTcd增加的发生率为45%,Child-Pugh C级患者的QT、QTc、QTd和QTcd均显著高于A级和B级患者。此外,该研究还表明相比于QT间期参数,QT离散度参数能更好预测死亡率^[63]。

10 小结

无论肝硬化病因如何,肝硬化患者的QT间期往往延长,病情加重的同时QT间期延长发生率增高,肝移植或给予 β -受体阻滞剂后QT间期将缩短。当肝硬化患者伴有消化道出血或需要进行肝移植等手术时,QT间期延长可能会危及生命,因此,如能及时有效纠正这一电生理异常,则有可能改善患者预后。遗憾的是,目前尚缺乏完善的治疗体系。未来的研究还应着重于QT间期延长的治疗,从发病机制出发的针对性治疗可能是其中一个方向。

作者贡献度说明:

撰写:李叶;资料收集:张露;指导专家:李生浩、王晴晴。
所有作者均声明不存在利益冲突。

参考文献

- 1 Hartl L, Rumpf B, Domenig O, et al. The systemic and hepatic alternative renin-angiotensin system is activated in liver cirrhosis, linked to endothelial dysfunction and inflammation[J]. Sci Rep, 2023, 13(1): 953.
- 2 Dourakis SP, Geladari E, Geladari C, et al. Cirrhotic cardiomyopathy: The interplay between liver and cardiac muscle. How does the cardiovascular system react when the liver is diseased? [J]. Curr Cardiol Rev, 2021, 17(1): 78-84.
- 3 Jahangiri S, Abdiardekani A, Jamshidi S, et al. Electrocardiographic characteristics of cirrhotic patients and their association with Child-Pugh score [J]. Clin Cardiol, 2023, 46(8): 967-972.
- 4 Lyssy LA, Soos MP. Cirrhotic cardiomyopathy [M]. Treasure Island (FL): StatPearls Publishing, 2024.
- 5 Bhardwaj A, Joshi S, Sharma R, et al. QTc prolongation in patients of cirrhosis and its relation with disease severity: An observational study from a rural teaching hospital [J]. J Family Med Prim Care, 2020, 9(6): 3020-3024.
- 6 Tieranu E, Donoiu I, Istrătoae O, et al. Q-T interval prolongation in patients with liver cirrhosis [J]. Curr Health Sci J, 2018, 44(3): 274-279.

- 7 Lee W, Vandenberk B, Raj SR, et al. Prolonged QT interval in cirrhosis: Twisting time?[J]. Gut Liver, 2022, 16(6): 849-860.
- 8 Zambruni A, Di Micoli A, Lubisco A, et al. QT interval correction in patients with cirrhosis[J]. J Cardiovasc Electrophysiol, 2007, 18(1): 77-82.
- 9 Głównczyńska R, Galas M, Ołdakowska-Jedynak U, et al. Pretransplant QT interval: The relationship with severity and etiology of liver disease and prognostic value after liver transplantation [J]. Ann Transplant, 2018, 23: 622-630.
- 10 Giudicessi JR, Noseworthy PA, Ackerman MJ. The QT interval [J]. Circulation, 2019, 139(24): 2711-2713.
- 11 Day CP, James OF, Butler TJ, et al. QT prolongation and sudden cardiac death in patients with alcoholic liver disease[J]. Lancet, 1993, 341(8858): 1423-1428.
- 12 Wang Z, Qian R, Wang Y, et al. QTc interval prolongation in the patients with primary biliary cholangitis [J]. Ann Noninvasive Electrocardiol, 2022, 27(1): e12925.
- 13 Lu L, Lv X, Wu Q, et al. Comparison of electrocardiogram and QT interval between viral hepatitis cirrhosis and alcoholic cirrhosis [J]. Cardiol Res Pract, 2022, 2022: 6934418.
- 14 Wang C, Gao H, Liu W, et al. Alcoholic cardiomyopathy in patients with alcoholic liver cirrhosis: A study across 10 years[J]. Eur J Gastroenterol Hepatol, 2023, 35(5): 600-603.
- 15 Papadopoulos VP, Mimidis K. Corrected QT interval in cirrhosis: A systematic review and meta-analysis [J]. World J Hepatol, 2023, 15(9): 1060-1083.
- 16 Bernardi M, Calandra S, Colantoni A, et al. Q-T interval prolongation in cirrhosis: Prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors [J]. Hepatology, 1998, 27(1): 28-34.
- 17 Izzy M, van Wagner LB, Lin G, et al. Redefining cirrhotic cardiomyopathy for the modern era[J]. Hepatology, 2020, 71(1): 334-345.
- 18 Koshy AN, Gow PJ, Testro A, et al. Relationship between QT interval prolongation and structural abnormalities in cirrhotic cardiomyopathy: A change in the current paradigm [J]. Am J Transplant, 2021, 21(6): 2240-2245.
- 19 Bilous Z, Abrahamovych O, Abrahamovych M, et al. Characteristics of the autonomic nervous system state, assessed by the heart rate variability study in cirrhotic patients with syntropic cardiomyopathy and its features depending on the QT interval duration [J]. Georgian Med News, 2023, 334: 78-82.
- 20 Yumusak O, Douberis M. Update on cirrhotic cardiomyopathy: From etiopathogenesis to treatment [J]. Ann Gastroenterol, 2024, 37(4): 381-391.
- 21 Yoon KT, Liu H, Lee SS. Cirrhotic cardiomyopathy [J]. Curr Gastroenterol Rep, 2020, 22(9): 45.
- 22 Abrahamovych M, Tolopko S, Farmaha M, et al. Criteria for diagnosis of cardiomyopathy in patients with alcoholic liver cirrhosis before the onset of heart damage clinical signs [J]. Georgian Med News, 2020, 300: 81-85.
- 23 王爱鱼, 侯培珍, 高军. 肝硬化所致心脏损害——附 96 例尸解分析 [J]. 中华消化杂志, 1998, 18(3): 184.
- 24 Wang A, Hou P, Gao J, et al. Cardiac damage caused by liver cirrhosis-with autopsy analysis of 96 cases [J]. Chin J Digest, 1998, 18(3): 184.
- 25 Gananandan K, Wiese S, Møller S, et al. Cardiac dysfunction in patients with cirrhosis and acute decompensation [J]. Liver Int, 2024, 44(8): 1832-1841.
- 26 Almeida F, Sousa A. Cirrhotic cardiomyopathy: Pathogenesis, clinical features, diagnosis, treatment and prognosis [J]. Rev Port Cardiol, 2024, 43(4): 203-212.
- 27 Trevisani F, Merli M, Savelli F, et al. QT interval in patients with non-cirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic porto-systemic shunt [J]. J Hepatol, 2003, 38(4): 461-467.
- 28 Deltente P, Zanetto A, Saltini D, et al. The role of transjugular intrahepatic portosystemic shunt in patients with cirrhosis and ascites: Recent evolution and open questions [J]. Hepatology, 2023, 77(2): 640-658.
- 29 Toma L, Stanciu AM, Zgura A, et al. Electrocardiographic changes in liver cirrhosis-clues for cirrhotic cardiomyopathy [J]. Medicina (Kaunas), 2020, 56(2): 68.
- 30 Al Sayed ZR, Pereira C, Le Borgne R, et al. Cavin1-mediated hERG dynamics: A novel mechanism underlying the interindividual variability in drug-induced long QT [J]. Circulation, 2024, 150(7): 563-576.
- 31 Tang JK, Rabkin SW. Hypocalcemia-induced QT interval prolongation [J]. Cardiology, 2022, 147(2): 191-195.
- 32 Zhao J, Qi X, Hou F, et al. Prevalence, risk factors and in-hospital outcomes of QTc interval prolongation in liver cirrhosis [J]. Am J Med Sci, 2016, 352(3): 285-295.
- 33 Kim SM, George B, Alcivar-Franco D, et al. QT prolongation is associated with increased mortality in end stage liver disease [J]. World J Cardiol, 2017, 9(4): 347-354.
- 34 张海霞. 肝炎肝硬化患者 QTc 间期、Tp-e 间期和 Tp-e/QT 的临床观察 [J]. 中华临床医师杂志 (电子版), 2012, 20: 6242-6245.

- Zhang H. The observation of QTc interval, Tp-e interval and Tp-e/QT ratio in ECG in patients with hepatitis and cirrhosis[J]. Chin J Clin (E Ed), 2012, 20: 6242-6245.
- 34 Henriksen JH, Fuglsang S, Bendtsen F, et al. Dyssynchronous electrical and mechanical systole in patients with cirrhosis[J]. J Hepatol, 2002, 36(4): 513-520.
- 35 Ruf A, Dirchwolf M, Freeman RB. From Child-Pugh to MELD score and beyond: Taking a walk down memory lane[J]. Ann Hepatol, 2021, 27(1): 100535.
- 36 Barutcu S, Inanc I, Sabanoglu C, et al. Predictive value of Tp-e interval, Tp-e/QT, and Tp-e/QTc for disease severity in patients with liver cirrhosis[J]. Eur Rev Med Pharmacol Sci, 2023, 27(3): 1110-1120.
- 37 Ou M, Tian Y, Zhuang G, et al. QTc interval prolongation in liver cirrhosis with upper gastrointestinal bleeding [J]. Med Clin (Barc), 2021, 156(2): 68-75.
- 38 Abbas WA, Kasem Ahmed SM, Abdel Aal AM, et al. Galactin-3 and brain natriuretic peptide versus conventional echocardiography in the early detection of cirrhotic cardiomyopathy [J]. Turk J Gastroenterol, 2016, 27(4): 367-374.
- 39 Biselli M, Gramenzi A, Lenzi B, et al. Development and validation of a scoring system that includes corrected QT interval for risk analysis of patients with cirrhosis and gastrointestinal bleeding [J]. Clin Gastroenterol Hepatol, 2019, 17(7): 1388-1397.e1.
- 40 Li S, Hao X, Liu S, et al. Prolonged QTc interval predicts long-term mortality in cirrhosis: A propensity score matching analysis[J]. Scand J Gastroenterol, 2021, 56(5): 570-577.
- 41 Trevisani F, Di Micoli A, Zambruni A, et al. QT interval prolongation by acute gastrointestinal bleeding in patients with cirrhosis[J]. Liver Int, 2012, 32(10): 1510-1515.
- 42 Kazankov K, Jensen HK, Watson H, et al. QT interval corrected for heart rate is not associated with mortality in patients with cirrhosis and ascites[J]. Scand J Gastroenterol, 2019, 54(11): 1376-1378.
- 43 Bal JS, Thuluvath PJ. Prolongation of QTc interval: Relationship with etiology and severity of liver disease, mortality and liver transplantation[J]. Liver Int, 2003, 23(4): 243-248.
- 44 Bodys-Pelka A, Kuształ M, Raszeja-wyszomirska J, et al. What's new in cirrhotic cardiomyopathy? -Review article[J]. J Pers Med, 2021, 11(12): 1285.
- 45 Kim YK, Hwang GS, Shin WJ, et al. Effect of propranolol on the relationship between QT interval and vagal modulation of heart rate variability in cirrhotic patients awaiting liver transplantation [J]. Transplant Proc, 2011, 43(5): 1654-1659.
- 46 Henriksen JH, Bendtsen F, Hansen EF, et al. Acute non-selective beta-adrenergic blockade reduces prolonged frequency-adjusted Q-T interval (QTc) in patients with cirrhosis [J]. J Hepatol, 2004, 40(2): 239-246.
- 47 Zambruni A, Trevisani F, Di Micoli A, et al. Effect of chronic beta-blockade on QT interval in patients with liver cirrhosis[J]. J Hepatol, 2008, 48(3): 415-421.
- 48 Alvarado-Tapias E, Ardevol A, Garcia-Guix M, et al. Short-term hemodynamic effects of β -blockers influence survival of patients with decompensated cirrhosis [J]. J Hepatol, 2020, 73(4): 829-841.
- 49 Han H, Chen J, Deng Z, et al. Propranolol can correct prolonged QT intervals in patients with cirrhosis [J]. Front Pharmacol, 2024, 15: 1370261.
- 50 Kim HM, Kim HK, Lee JH, et al. Myocardial structural and functional changes in patients with liver cirrhosis awaiting liver transplantation: A comprehensive cardiovascular magnetic resonance and echocardiographic study [J]. J Cardiovasc Magn Reson, 2020, 22(1): 25.
- 51 Koshy AN, Ko J, Farouque O, et al. Impact of liver transplantation on QT-interval in patients with cirrhosis [J]. J Am Coll Cardiol, 2020, 75(11): 398.
- 52 Ko J, Koshy AN, Han HC, et al. Effect of liver transplantation on QT-interval prolongation and impact on mortality[J]. Int J Cardiol, 2021, 326: 158-163.
- 53 Flaherty D, Kim S, Zerillo J, et al. Preoperative QTc interval is not associated with intraoperative cardiac events or mortality in liver transplantation patients[J]. J Cardiothorac Vasc Anesth, 2019, 33(4): 961-966.
- 54 张晓雪, 金清龙, Glannelli V, 等. 心功能、难治性腹水和 β 受体阻滞剂对行肝移植的肝硬化患者预后的影响 [J]. 临床肝胆病杂志, 2020, 36(3): 630.
- Zhang X, Jin Q, Glannelli V, et al. Impact of cardiac function, refractory ascites and β blockers on the outcome of patients with cirrhosis listed for liver transplantation [J]. J Clin Hepatol, 2020, 36(3): 630.
- 55 Koshy AN, Ko J, Farouque O, et al. Effect of QT interval prolongation on cardiac arrest following liver transplantation and derivation of a risk index[J]. Am J Transplant, 2021, 21(2): 593-603.
- 56 Salgado AA, Barbosa PR, Ferreira AG, et al. Prognostic value of a new marker of ventricular repolarization in cirrhotic patients[J]. Arq Bras Cardiol, 2016, 107(6): 523-531.
- 57 Tuttolomondo A, Buttà C, Casuccio A, et al. QT indexes in cirrhotic patients: Relationship with clinical variables and potential diagnostic predictive value [J]. Arch

- Med Res, 2015, 46(3): 207-213.
- 58 Hansen S, Møller S, Bendtsen F, et al. Diurnal variation and dispersion in QT interval in cirrhosis: Relation to haemodynamic changes[J]. J Hepatol, 2007, 47(3): 373-380.
 - 59 Huh IY, Park ES, Kim KI, et al. Alteration of the QT variability index in end-stage liver disease[J]. Korean J Anesthesiol, 2014, 66(3): 199-203.
 - 60 Zamirian M, Tavassoli M, Aghasadeghi K. Corrected QT interval and QT dispersion in cirrhotic patients before and after liver transplantation[J]. Arch Iran Med, 2012, 15(6): 375-377.
 - 61 Aroorva M, Atkar C. A study on QT dispersion before and after thrombolysis in acute myocardial infarction, and its prognostic implications[J]. J Assoc Physicians India, 2022, 70(4): 11-12.
 - 62 Moaref A, Zamirian M, Mirzaei H, et al. Myocardial contractile dispersion: A new marker for the severity of cirrhosis? [J]. J Cardiovasc Thorac Res, 2019, 11(2): 147-151.
 - 63 Kosar F, Ates F, Sahin I, et al. QT interval analysis in patients with chronic liver disease: A prospective study [J]. Angiology, 2007, 58(2): 218-224.

[本文编辑] 谭贝加 宋睿璞 陈思润

+++++

(上接第 633 页)

- 42 Kureishi Y, Luo Z, Shiojima I, et al. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase AKT and promotes angiogenesis in normocholesterolemic animals[J]. Nat Med, 2000, 6(9): 1004-1010.
- 43 Asai J, Takenaka H, Hirakawa S, et al. Topical simvastatin accelerates wound healing in diabetes by enhancing angiogenesis and lymphangiogenesis [J]. Am J Pathol, 2012, 181(6): 2217-2224.
- 44 Zhao T, Trinh D, Addison CL, et al. Lovastatin inhibits VEGFR and AKT activation: Synergistic cytotoxicity in combination with VEGFR inhibitors [J]. PLoS One, 2010, 5(9): e12563.
- 45 Duester G. Retinoic acid synthesis and signaling during early organogenesis[J]. Cell, 2008, 134(6): 921-931.
- 46 Marino D, Dabouras V, Brändli AW, et al. A role for all-trans-retinoic acid in the early steps of lymphatic vasculature development [J]. J Vasc Res, 2010, 48(3): 236-251.
- 47 Zhu J, Luo Y, Zhao Y, et al. circEHBP1 promotes lymphangiogenesis and lymphatic metastasis of bladder cancer *via* miR-130a-3p/TGFβR1/VEGF-D signaling [J]. Mol Ther, 2021, 29(5): 1838-1852.
- 48 Renò F, Sabbatini M. Breaking a vicious circle: Lymphangiogenesis as a new therapeutic target in wound healing[J]. Biomedicines, 2023, 11(3): 656.
- 49 Wu M, Liu Q, Yu Z, et al. Negative-pressure wound therapy induces lymphangiogenesis in murine diabetic wound healing[J]. Plast Reconstr Surg, 2023, 151(4): 779-790.
- 50 Wu M, Matar DY, Yu Z, et al. Modulation of lymphangiogenesis in incisional murine diabetic wound healing using negative pressure wound therapy [J]. Adv Wound Care (New Rochelle), 2023, 12(9): 483-497.

[本文编辑] 谭贝加 宋睿璞 陈思润