论著·公共卫生智库

残余胆固醇的变异性与心脏传导阻滞风险的U型关联

曹柳柳[1,2*],李 曼[3*],武朝辉[4],郑维国[1],王宝华[5],张 丽[1],赵茂林[1],李 鹏[1],赵海燕[6],陈朔华[6],吴寿岭[6],孙丽霞[1] 华北理工大学附属医院:[1]急诊科,[5]重症医学科,河北唐山;[2]华北理工大学研究生院,河北唐山;[3]暨南大学第一附属医院重症医学科,广东广州;[4]山西医科大学研究生院,山西太原;[6]开滦总医院心血管内科,河北唐山

[**摘要**] **目的** 本研究基于开滦队列,探讨长期随访期间残余胆固醇(remnant cholesterol,RC)的变异性与心脏传导阻滞(cardiac conduction block,CCB)的关联。**方法** 采用回顾性队列研究,以连续参加2006、2008、2010年度体检的开滦研究人群作为研究队列,根据纳入和排除标准,最终入选39 299例观察对象,计算随访期间RC的变异性,RC的变异性通过标准差(standard deviation,SD)、平均真实变异性(average real variability,ARV)、变异系数(coefficient of variation,CV)、独立于均值的变异(variation independent of mean,VIM)测量。以RC的变异性四分位进行分组,将观察对象分成4组,每2年进行1次随访,以发生CCB、死亡或随访结束(2019年12月31日)为随访终点,采用Kaplan-Meier法计算不同分组发生终点事件的累积发病率,并用Log-Rank检验比较各组终点事件累积发生率的差异。用Cox比例风险模型及限制性立方样条曲线(restricted cubic spline, RCS)分析RC的变异性与CCB及其亚型的关联。**结果** 39 299例观察对象在平均随访7.43年后,发生CCB者共916人。以CCB为结局事件,校正混杂因素后,以RC-SD四分位分组,与RC-SD最低发病密度组(Q2)相比,Q1组发生CCB的*HR*值为1.344(95%*CI*:1.110~1.626,*P*=0.002),Q3、Q4组发生CCB的*HR*值分别1.068(95%*CI*:0.878~1.299,*P*=0.509)、1.311(95%*CI*:1.089~1.579,*P*=0.004)。以RC-ARV、RC-CV、RC-VIM四分位分组均得出类似的结论。RCS曲线表明,RC-SD与CCB之间呈U型关联($P_{overall}$<0.05, $P_{nonlinearity}$<0.05)。敏感性分析、分层分析进一步验证了此结论。**结论** RC的变异性与CCB呈U型关联,该研究为预防CCB的发生提供了新的方向。**对策** 我国血脂管理策略应从追求“低水平稳定”,向兼顾“指标长期平稳性”转型升级。即将“维持血脂在适宜区间的生理性波动”这一新理念,系统整合至国家心脑血管疾病防治规划、基层公共卫生服务项目及全民健康教育体系,以此推动慢性病管理迈向更加精准、科学的新阶段。

[**关键词**] 心脏传导阻滞;残余胆固醇;变异性

[**中图法分类号**] R181.37;R344.81;R541.76 [**文献标志码**] A

[**基金项目**] 河北省重点研发计划项目(19277791D)

* 同等贡献者

[**通信作者**] 孙丽霞,E-mail:13323151999@189.cn

吴寿岭,E-mail:drwusl@163.com

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引用格式:曹柳柳,李曼,武朝辉,等. 残余胆固醇的变异性与心脏传导阻滞风险的U型关联[J]. 陆军军医大学学报,2026,48(02):216-228. DOI:10.16016/j.2097-0927.202510061.

Citation:CAO L L, LI M, WU Z H, *et al*. U-shaped association between variability of remnant cholesterol and risk of cardiac conduction block[J]. J Army Med Univ,2026,48(02):216-228. DOI:10.16016/j.2097-0927.202510061.

U-shaped association between variability of remnant cholesterol and risk of cardiac conduction block

CAO Liuliu[1,2*], LI Man[3*], WU Zhaohui[4], ZHENG Weiguo[1], WANG Baohua[5], ZHANG Li[1], ZHAO Maolin[1], LI Peng[1], ZHAO Haiyan[6], CHEN Shuohua[6], WU Shouling[6], SUN Lixia[1] [1]Department of Emergency, [5]Department of Intensive Care Unit, Affiliated Hospital of North China University of Science and Technology, Tangshan, Hebei; [2]Graduate School, North China University of Science and Technology, Tangshan, Hebei; [3]Department of Intensive Care Unit, the First Affiliated Hospital of Jinan University, Guangzhou, Gaungdong; [4]Graduate School, Shanxi Medical University, Taiyuan, Shanxi; [6]Department of Cardiovascular Medicine, Kailuan General Hospital, Tangshan, Hebei, China

[**Abstract**] Objective To investigates the association between the variability of remnant cholesterol (RC) during long-term follow-up and cardiac conduction block (CCB) based on the Kailuan cohort. Methods A retrospective study was conducted on the research cohort in the Kailuan study population who consecutively participated in the physical examinations of 2006, 2008, and 2010. Based on the inclusion and exclusion criteria, 39 299 subjects were ultimately enrolled in the study. The variability of RC during the follow-up period was calculated, with the variability assessed through standard deviation (SD), average real variability (ARV), coefficient of variation (CV), and variability independent of the mean (VIM). The participants were divided into 4 groups based on the interquartile range of RC variability, and followed up every 2 years. The endpoints were defined as the occurrence of CCB, death, or the termination of follow-up (December 31, 2019). Kaplan-Meier test and Log-Rank test were carried out respectively calculate and compare the cumulative incidence rate of endpoint events across groups. Cox proportional hazards model and restricted cubic spline (RCS) analysis were performed to analyze the association between the variability of RC and CCB and its subtypes. Results After an average follow-up of 7.43 years in 39 299 participants, 916 patients developed CCB. After adjusting for confounding factors, using CCB as the outcome event, and were dividing the participants into groups based on the RC-SD quartiles, the hazard ratios (*HR*) for CCB occurrence were 1.344 in the Q1 group (95% *CI*: 1.110~1.626, *P*=0.002), 1.068 (95% *CI*: 0.878 to 1.299, *P*=0.509) in the Q3 group and 1.311 (95% *CI*: 1.089~1.579, *P*=0.004) in the Q4 group, when compared to the group of lowest incidence density (the Q2 group). Similar results were obtained for the quartiles of RC-ARV, RC-CV, and RC-VIN grouping. RCS analysis revealed a U-shaped association between RC-SD and CCB ($P_{overall}$<0.05, $P_{nonlinearity}$<0.05). Sensitivity and stratified analyses further validated this finding. Conclusion There exists a U-shaped association between the variability of RC and the risk of CCB. This finding provides a new direction for preventing the occurrence of CCB. Countermeasures China's blood lipid management strategy should undergo a paradigm shift from pursuing "low-level stability" toward integrating "long-term stability of biomarker levels" This entails systematically incorporating the new concept of "maintaining physiological fluctuations of blood lipids within an optimal range" into the national prevention and treatment plans for cardiovascular and cerebrovascular diseases, primary public health service programs, and the public health education system. Such a transition will propel chronic disease management into a more precise and scientific new stage.

[**Key words**] cardiac conduction block; remnant cholesterol; variability

CAO Liuliu and LI Man contributed equally to the article. Supported by the Project of Key Research and Development Program of Hebei Province (19277791D). Corresponding authors: SUN Lixia, E-mail: 13323151999@189.cn; WU Shouling, E-mail: drwusl@163.com

心脏传导阻滞(cardiac conduction block,CCB)是一种缓慢性心律失常,其特征在于心脏电冲动在心脏传导系统中的延迟或完全中断,包括窦房传导阻滞、房室传导阻滞(atrioventricular block,AVB)以及束支传导阻滞(bundle branch block,BBB)[1-2]。2018年,我国人群AVB的患病率约为0.706%,其中,1度AVB的患病率为0.684%,2度AVB的患病率为0.018%,3度AVB的患病率为0.004%[3]。在芬兰的普通人群中,1度AVB的患病率为2%[4]。尽管传导阻滞的患病率较低,但是仍有可能出现心室颤动、心力衰竭、甚至是心脏骤停等危及生命的严重并发症[5-7]。虽然起搏器的植入可缓解CCB的症状,但目前尚无有效根治CCB的策略。因此,早期识别其危险因素极为重要。

残余胆固醇(remnant cholesterol,RC)是指富含甘油三酯的脂蛋白胆固醇含量,包括空腹状态下的极低密度脂蛋白胆固醇和中间密度脂蛋白胆固醇以及非空腹状态下的乳糜微粒[8]。RC的变异性可以反映其较长时间的波动情况,从而更好地预测心血管事件的发生。一项来自美国的ARIC研究显示,以RC-ARV四分位分组,在校正相关协变量后,与最低四分位组相比,最高四分位组发生房颤的风险增加了30%[9]。ACCORD研究发现,在调整传统心血管危险因素后,RC变异性高的组发生主要不良心血管事件(major adverse cardiovascular events,MACE)的风险增加了约40%[10]。但目前尚缺乏RC及其变异性与缓慢性心律失常的关联性研究。因此,本研究基于开滦队列研究,探讨RC的变异性与CCB的关联,以期为CCB的预防提供参考。

1 资料与方法

1.1 研究对象

开滦研究是一项以唐山市开滦社区为基础的前瞻性队列研究(注册号:ChiCTR-TNC-11001489),详细的研究设计在前期研究中已充分描述[11-12]。该项目始于2006—2007年,由开滦总医院及其所属11家附属医院对开滦集团公司在职及离退休职工共101 510人进行第1次健康体检及问卷调查,此后每2年进行1次随访调查并邀请新入职员工参与。该项研究招募了101 510名参与者,其中包括男性81 110名,女性20 400名,均签署知情同意书。本研究选取连续参加2006—2007、2008—2009、2010—2011年3次健康体检者58 869名,排除了3次体检中RC数据缺失者14 485名,CCB病史者2 505名以及心电图数据缺失者2 580名后,最终纳入39 299名研究对象。本研究遵照赫尔辛基宣言,并获得开滦总医院伦理委员会审批许可([2006]医伦字5号)。

1.2 资料收集

体检者需空腹8 h,由专业人员抽取肘静脉血5 mL于EDTA真空管内,在室温下经3 000 r/min离心10 min后,取上层血清进行生化指标检测,总胆固醇(total cholesterol, TC)、高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)和低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)采用酶比色法进行测定,并根据公式(RC=TC−HDL-C−LDL-C)计算RC的值[13]。RC的变异性采用4个指标:①标准差(standard deviation,SD):$SD=\sqrt{\frac{1}{n-1}\sum_{i-1}^{n}\left(x_i-\bar{x}\right)^2}$;②平均真实变异性(average real variability, ARV):$ARV=\frac{1}{N-1}\sum_{K-1}^{N-1}=|Value_{K+1}-Value_K|$;③变异系数(coefficient of variation,CV):变异系数=(标准差/均数)×100%;④独立于均值的变异(variation independent of mean, VIM):VIM=标准差/平均值^x(X通过计算变异系数变化曲线与平均RC变化曲线的拟合程度计算,由SAS软件Proc NLIN程序中的非线性回归分析拟合曲线得到)。

将RC的变异性按四分位进行分组:第一四分位组(RC-SD<0.325, RC-ARV<0.381, RC-CV<37.300,或RC-VIM<0.417),第二四分位组(RC-SD:0.325~0.565,RC-ARV:0.381~0.673,RC-CV:37.300~57.135,RC-VIM:0.417~0.636),第三四分位组(RC-SD:0.565~0.849,RC-ARV:0.673~1.049,RC-CV:57.135~76.083,RC-VIM:0.636~0.849),第四四分位组(RC-SD≥0.849,RC-ARV≥1.049,RC-CV≥76.083,RC-VIM≥0.849)。

心电图测量要求受试者在安静的房间里舒适地以仰卧姿势休息5 min后,进行连续10 s的12导联心电图检查。各种CCB根据《明尼苏达法典》心电图诊断标准和美国心脏协会指南进行定义。CCB分为多种类型,包括AVB、BBB,BBB包括右束支传导阻滞(right bundle branch block,RBBB)和左束支传导阻滞(left bundle branch block,LBBB),其中RBBB包括完全性右束支传导阻滞(complete right bundle branch block,CRBBB)和不完全性右束支传导阻滞(incomplete right bundle branch block,iRBBB),LBBB包括不完全性左

束支传导阻滞(incomplete left bundle branch block,iLBBB)、左前分支传导阻滞(left anterior fascicular block,LAPB)、左后分支传导阻滞(left posterior fascicular block,LPFB)和非特异性室内传导阻滞(nonspecific intraventricular conduction block,NS-IVCB)。心电图测量和诊断由2名心电图专家完成,所有参与者从基线开始每2年进行1次测量,直到终点事件发生或随访结束。

研究对象的年龄、性别、吸烟、饮酒、体力活动(非常活跃、中等活跃、不活跃)、打鼾、疾病史以及服药史是通过面对面访谈和问卷调查获得。体格检查主要包括研究对象的身高、体质量、收缩压(systolic blood pressure, SBP)、舒张压(diastolic blood pressure, DBP),并计算体质指数(body mass index, BMI),具体的测量方法已在前期研究中进行了详细描述[14]。实验室检查包括研究对象的高敏C反应蛋白(high-sensitivity C-reactive protein,hs-CRP)、空腹血糖(fasting blood glucose, FBG)、血肌酐(serum creatinine, SCr)、甘油三酯(triglyceride, TG)、TC、HDL-C和LDL-C,所有生化变量均使用日立747全自动生化分析仪进行测量。

1.3 相关定义

吸烟定义为近1年平均每天至少吸1支烟,连续吸烟1年以上。饮酒定义为近1年平均每日饮酒(酒精含量50%以上)100 mL,连续1年以上。高血压定义为SBP≥140 mmHg和(或)DBP≥90 mmHg,或SBP<140 mmHg和DBP<90 mmHg,但有高血压病史或正在服用降压药[15]。糖尿病定义为FBG≥7.0 mmol/L或FBG<7.0 mmol/L但有糖尿病病史或正在服用降糖药[16]。高脂血症定义为血清TC≥6.2 mmol/L或HDL-C<1.0 mmol/L或LDL-C≥4.1 mmol/L或TG≥2.3 mmol/L或有高血脂病史或正在服用降脂药[17]。估算的肾小球滤过率(estimated glomerular filtration rate,eGFR)采用慢性肾脏病学流行病学合作研究(chronic kidney disease epidemiology collaboration, CKD-EPI)公式计算[18]。

1.4 随访和终点事件

以完成2010年度体检的时间为随访起点,以发生CCB、死亡或随访结束(2019年12月31日)为随访终点,共计39 299名观察对象完成了(7.43±2.14)年的随访。

1.5 统计学分析

采用SAS 9.4软件进行统计分析,符合正态分布的计量资料采用$\bar{x}\pm s$表示,组间比较采用方差分析;非正态分布的计量资料采用$M(P_{25},P_{75})$表示,组间比较采用非参数秩和检验(Kruskal-Wallis);计数资料用例(%)来表示,组间比较采用χ^2检验;以事件数除以随访总人年(1 000/人年)分别计算不同RC变异性组别发生CCB的发病密度,采用Kaplan-Meier法计算不同分组发生终点事件的累积发病率,组间比较采用Log-Rank检验;采用多因素Cox比例风险回归模型分别分析RC变异性不同分组对终点事件的发生风险及95%可信区间,以$P<0.05$(双侧检验)为差异有统计学意义。模型1校正年龄、性别;模型2在模型1的基础上校正吸烟、饮酒、体力活动、BMI;模型3在模型2的基础上校正hs-CRP、eGFR、高血压、糖尿病、高脂血症、打鼾、降压药、降糖药、降脂药;模型4在模型3的基础上校正2010年的RC;模型5在模型3的基础上校正2006年的RC。采用3节点(第25、50、75百分位)RCS曲线图进一步研究RC的变异性与CCB的剂量-反应关系,RCS曲线图中校正模型4中的校正变量。为保证结果的稳健性,进行敏感性分析:①排除随访2年内即发生CCB的人群。②排除基线及随访时发生心衰及急性心肌梗死的人群。③排除使用降脂药的人群。④使用Fine-Gray模型进行死亡竞争风险分析。同时对性别(男性,女性)、年龄(<55岁,≥55岁)、高血压(是,否)、糖尿病(是,否)进行分层分析。

2 结果

2.1 研究对象的基本特征

根据纳排标准,最终纳入39 299名观察对象,其中,男性30 537名(77.7%),女性8 762名(22.3%),年龄(54.9±12.4)岁。表1为参与者的基线特征,Q4组与Q2组相比年龄、TC、hs-CRP、RC、eGFR较高,且患心衰、心梗、高血压、糖尿病、高血脂的人数较多,服用降压药、降糖药、降脂药的人数也较多。

2.2 RC的变异性与CCB及其亚型的累积发生率

在中位随访7.43年期间,共发生了916例CCB事件,发病密度为3.14/千人年(95%*CI*: 2.94~3.35)。对于CCB亚型,AVB、BBB、RBBB和LBBB分别发生301、594、456和207例。各组间累积发病率差异有统计学意义($P_{log-rank}<0.05$,图1)。

表1 以RC-SD分组研究对象的基线特征[$\bar{x}\pm s$, $M(P_{25},P_{25})$,例(%)]

Table 1 Baseline characteristics of the participants grouped according to RC-SD[$\bar{x}\pm s$, $M(P_{25},P_{25})$, n(%)]

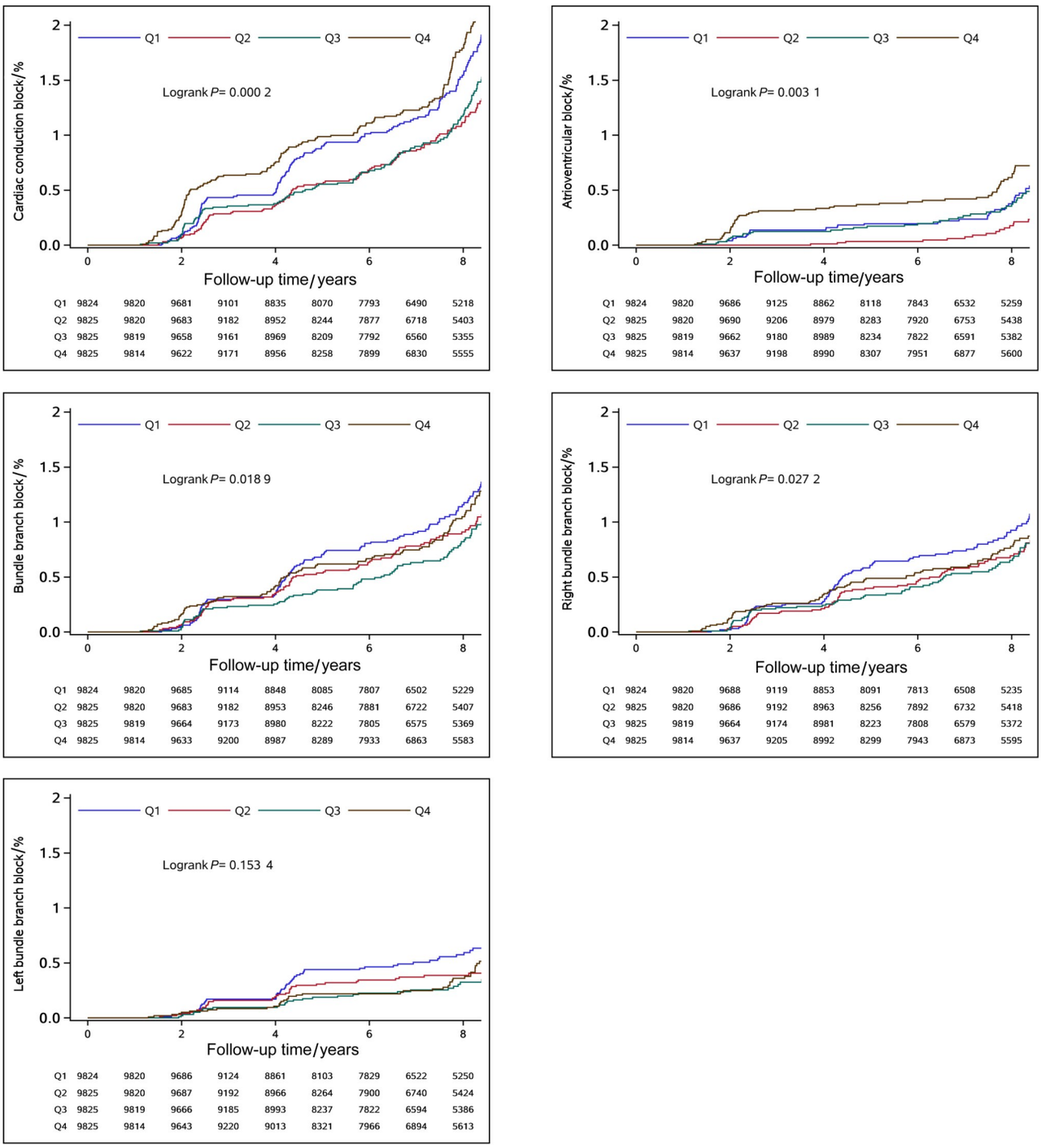
Factors	Total (n=39 299)	Q1 (n=9 824)	Q2 (n=9 825)	Q3 (n=9 825)	Q4 (n=9 825)
RC-SD/(mmol/L)	0.6(0.3~0.8)	0.2(0.1~0.3)	0.4(0.4~0.5)	0.7(0.6~0.8)	1.1(1.0~1.4)
Age/years	54.9±12.4	55.4±13.2	54.2±12.4	54.0±11.7	56.1±12.0
Male	30537(77.7)	7770(79.1)	7630(77.7)	7611(77.5)	7526(76.6)
Total cholesterol/(mmol/L)	5.1±1.0	4.9±0.9	5.0±0.9	5.1±0.9	5.4±1.2
Low density lipoprotein cholesterol/(mmol/L)	2.6±0.8	2.7±0.7	2.6±0.7	2.6±0.8	2.4±1.0
High density lipoprotein cholesterol/(mmol/L)	1.5(1.2~1.8)	1.5(1.2~1.8)	1.4(1.2~1.7)	1.5(1.2~1.8)	1.5(1.2~1.8)
Remnant cholesterol/(mmol/L)	0.7(0.4~1.4)	0.6(0.4~1.0)	0.8(0.4~1.3)	0.7(0.4~1.5)	1.0(0.4~2.3)
hs-CRP/(mg/L)	1.2(0.5~2.7)	1.2(0.5~2.7)	1.1(0.5~2.4)	1.1(0.6~2.6)	1.3(0.6~3.1)
eGFR/[mL/(min·1.73m^2)]	89.5±20.4	86.3±21.6	89.8±20.6	91.4±18.9	90.5±19.9
Current smoker	13 433(34.2)	3 352(34.1)	3 554(36.2)	3 436(35.0)	3 091(31.5)
Current drinker	13 952(35.5)	3 473(35.4)	3 748(38.1)	3 585(36.5)	3 146(32.0)
Physical activity	5 708(14.5)	1 167(11.9)	1 476(15.0)	1 613(16.4)	1 452(14.8)
Snorer	15 999(40.7)	3 747(38.1)	4 183(42.6)	4 202(42.8)	3 867(39.4)
Body mass index/(kg/m^2)					
Normal/underweight(<24 kg/m^2)	15 830(40.3)	4 010(40.8)	3 855(39.2)	4 036(41.1)	3 929(40.0)
Overweight(24~28 kg/m^2)	16 434(41.8)	4 065(41.4)	4 216(42.9)	4 024(41.0)	4 129(42.0)
Obese(>28 kg/m^2)	7 035(17.9)	1 749(17.8)	1 754(17.9)	1 765(18.0)	1 767(18.0)
Hypertension	18 069(46.0)	4 146(42.2)	4 560(46.4)	4 640(47.2)	4 723(48.1)
Diabetes	4 308(11.0)	922(9.4)	1 009(10.3)	1 103(11.2)	1 274(13.0)
Hyperlipemia	13 597(34.6)	2 617(26.6)	3 469(35.3)	3 435(35.0)	4 076(41.5)
Baseline and follow-up for heart failure	580(1.5)	129(1.3)	121(1.2)	147(1.5)	183(1.9)
Baseline and follow-up for myocardial infarction	1 145(2.9)	241(2.5)	281(2.9)	293(3.0)	330(3.4)
Antihypertensive drugs	9 521(24.2)	2 133(21.7)	2 224(22.6)	2 460(25.0)	2 704(27.5)
Hypoglycemic drugs	3 017(7.7)	641(6.5)	700(7.1)	773(7.9)	903(9.2)
Lipid-lowering drugs	1 030(2.6)	198(2.0)	257(2.6)	236(2.4)	339(3.5)
RC-ARV	0.7(0.4~1.0)	0.2(0.2~0.3)	0.5(0.4~0.7)	0.8(0.7~1.0)	1.4(1.0~1.8)
RC-CV	58.4±28.3	31.0±17.9	51.8±19.4	66.8±20.0	84.0±23.9
RC-VIM	0.7±0.3	0.4±0.2	0.6±0.2	0.7±0.2	0.9±0.3

RC: Remnant cholesterol; SD: Standard deviation; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; ARV: Average real variability; CV: Coefficient of variation; VIM: Variability independent of the mean

2.3 RC的变异性与CCB及其亚型的Cox风险回归模型

与最低发病密度(Q2组)相比,较低和较高的RC变异性均能增加CCB的发生风险。校正年龄、性别、吸烟、饮酒、体育锻炼、BMI、eGFR、高血压、糖尿病、高血脂、hs-CRP、打鼾、降压药、降糖药、降脂药、2010年的RC后,Q1组发生CCB的*HR*值为1.344(95%*CI*:1.110~1.626);Q3组和Q4组发生CCB的*HR*值分别为1.068(95%*CI*:0.878~1.299)和1.311(95%*CI*:1.089~1.579)。见表2。RCS曲线图显示RC-SD与CCB呈U型关联($P_{\text{non-linearity}}$<0.05),见图2。对于CCB亚型,AVB、BBB和RBBB中观察到类似的结果,在LBBB中虽趋势一致,但结果差异无统计学意义,见表2。

此外,以RC-ARV四分位分组为自变量,对CCB进行Cox回归分析。校正年龄、性别、吸烟、饮酒、体育锻炼、BMI、eGFR、高血压、糖尿病、高血脂、hs-CRP、打鼾、降压药、降糖药、降脂药后,结果显示:与最低发病密度组(Q3)相比,Q1组和Q2组*HR*值分别为1.126

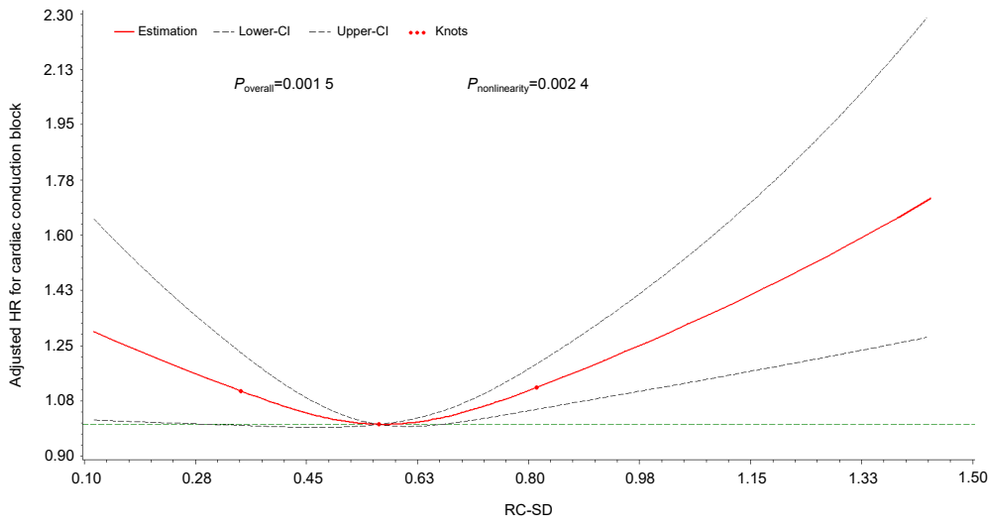


RC: remnant cholesterol; SD: standard deviation

图1 以RC-SD分组的RC变异性与CCB的累积发病率曲线

Figure 1 Cumulative incidence of cardiac conduction block and its subtypes according to RC-SD

(95%*CI*: 0.929~1.365)和1.112(95%*CI*: 0.920~1.345); Q4组*HR*值为1.252(95%*CI*: 1.041~1.505),但在此基础上校正2010年及2006年的RC后,虽然趋势未变但结果无统计学差异。此外,分别以RC-CV、RC-VIM四分位分组为自变量,对CCB进行Cox回归分析,结果虽无统计学意义,但与RC-SD趋势一致,见表3。



RC: remnant cholesterol; SD: standard deviation; CCB: cardiac conduction block; $P_{overall}$<0.05, $P_{nonlinearity}$<0.05

图2 以RC-SD分组的RC的变异性与CCB的RCS曲线

Figure 2 Associations of variability of RC with risk of CCB using restricted cubic spline regression model

表2 以RC-SD分组的残余胆固醇变异性与心脏传导阻滞及其亚型的关联

Table 2 Associations between variability of RC and risk of CCB and its subtypes stratified by RC-SD

Factors	*HR* (95% *CI*)			
	Q1	Q2	Q3	Q4
Cardiac conduction block, event/Total	237/9 824	198/9 825	207/9 825	274/9 825
Incidence density/1 000 person-years	3.289	2.696	2.838	3.732
Model 1	1.281(1.061~1.548)	Ref.	1.080(0.889~1.313)	1.384(1.152~1.662)
Model 2	1.291(1.068~1.559)	Ref.	1.083(0.892~1.317)	1.397(1.163~1.678)
Model 3	1.274(1.053~1.540)	Ref.	1.082(0.890~1.315)	1.390(1.156~1.671)
Model 4	1.344(1.110~1.626)	Ref.	1.068(0.878~1.299)	1.311(1.089~1.579)
Model 5	1.209(0.997~1.467)	Ref.	1.108(0.907~1.353)	1.441(1.180~1.759)
Atrioventricular block, event/Total	75/9 824	51/9 825	84/9 825	91/9 825
Incidence density/1 000 person-years	1.037	0.692	1.149	1.235
Model 1	1.598(1.119~2.282)	Ref.	1.714(1.210~2.427)	1.805(1.281~2.545)
Model 2	1.625(1.137~2.320)	Ref.	1.730(1.221~2.450)	1.848(1.310~2.606)
Model 3	1.673(1.170~2.391)	Ref.	1.714(1.210~2.428)	1.840(1.303~2.597)
Model 4	1.720(1.202~2.462)	Ref.	1.718(1.212~2.435)	1.799(1.272~2.544)
Model 5	1.619(1.128~2.325)	Ref.	1.707(1.195~2.439)	1.824(1.262~2.638)
Bundle branch block, event/Total	162/9 824	149/9 825	121/9 825	162/9 825
Incidence density/1 000 person-years	2.245	2.029	1.657	2.200
Model 1	1.377(1.087~1.743)	1.195(0.940~1.519)	Ref.	1.288(1.017~1.631)
Model 2	1.382(1.091~1.750)	1.194(0.939~1.518)	Ref.	1.295(1.022~1.640)
Model 3	1.338(1.055~1.698)	1.194(0.939~1.518)	Ref.	1.290(1.018~1.635)
Model 4	1.432(1.126~1.822)	1.214(0.954~1.544)	Ref.	1.234(0.972~1.565)
Model 5	1.226(0.954~1.574)	1.159(0.905~1.483)	Ref.	1.310(1.030~1.665)
Right bundle branch block, event/Total	133/9 824	112/9 825	96/9 825	115/9 825
Incidence density/1 000 person-years	1.842	1.523	1.314	1.561
Model 1	1.421(1.092~1.849)	1.130(0.860~1.484)	Ref.	1.159(0.883~1.521)
Model 2	1.428(1.097~1.859)	1.128(0.859~1.482)	Ref.	1.165(0.888~1.529)
Model 3	1.383(1.060~1.803)	1.123(0.855~1.476)	Ref.	1.165(0.887~1.530)
Model 4	1.444(1.104~1.888)	1.133(0.862~1.489)	Ref.	1.128(0.858~1.482)
Model 5	1.331(1.005~1.764)	1.132(0.854~1.501)	Ref.	1.154(0.876~1.521)

续表2 以RC-SD分组的残余胆固醇变异性与心脏传导阻滞及其亚型的关联

Table 2(Continued) Associations between variability of RC and risk of CCB and its subtypes stratified by RC-SD

Factors	*HR* (95% *CI*)			
	Q1	Q2	Q3	Q4
Left bundle branch block, event/Total	59/9 824	53/9 825	39/9 825	56/9 825
Incidence density/1 000 person-years	0.816	0.721	0.533	0.759
Model 1	1.505(1.003~2.257)	1.326(0.877~2.005)	Ref.	1.316(0.874~1.983)
Model 2	1.481(0.987~2.224)	1.334(0.882~2.018)	Ref.	1.294(0.859~1.951)
Model 3	1.330(0.882~2.006)	1.318(0.871~1.995)	Ref.	1.302(0.863~1.963)
Model 4	1.456(0.961~2.206)	1.363(0.900~2.065)	Ref.	1.240(0.820~1.875)
Model 5	1.036(0.673~1.594)	1.147(0.750~1.753)	Ref.	1.418(0.933~2.156)

Model 1: Adjusted for age and sex; Model 2: Adjusted for variables in model 1 and smoking, alcohol consumption, body mass index, and physical activity; Model 3: Adjusted for variables in model 2 and diabetes, hypertension, hyperlipemia, eGFR, hs-CRP, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs; Model 4: Adjusted for variables in model 3 and RC in 2010; Model 5: Adjusted for variables in model 3 and RC in 2006. RC: Remnant cholesterol; SD: Standard deviation; hs-CRP: High-sensitivity C-reactive protein; eGFR: Estimated glomerular filtration rate; CCB: Cardiac conduction block; Ref: reference; HR: Hazard ratio; CI: Confidence interval

表3 以RC-ARV、RC-CV、RC-VIM分组的残余胆固醇变异性与心脏传导阻滞的关联

Table 3 The association between variability of remnant cholesterol and risk of CCB by RC-ARV, RC-CV and RC-VIM

Factors	*HR* (95% *CI*)			
	Q1	Q2	Q3	Q4
RC-ARV	<0.381	0.381~0.673	0.673~1.049	≥1.049
Event/Total	222/9 824	227/9 825	202/9 825	265/9 825
Incidence density/1 000 person-years	3.083	3.123	2.755	3.589
Model 1	1.143(0.944~1.383)	1.123(0.929~1.358)	Ref.	1.246(1.037~1.497)
Model 2	1.149(0.949~1.391)	1.119(0.926~1.353)	Ref.	1.253(1.043~1.506)
Model 3	1.126(0.929~1.365)	1.112(0.920~1.345)	Ref.	1.252(1.041~1.505)
Model 4	1.189(0.980~1.443)	1.114(0.921~1.347)	Ref.	1.159(0.962~1.395)
Model 5	1.075(0.879~1.316)	1.110(0.915~1.347)	Ref.	1.240(1.031~1.491)
RC-CV	<37.300	37.300~57.135	57.135~76.083	≥76.083
Event/Total	242/9824	204/9825	244/9825	226/9825
Incidence density/1 000 person-years	3.375	2.791	3.307	3.084
Model 1	1.244(1.033~1.499)	Ref.	1.187(0.985~1.429)	1.109(0.918~1.340)
Model 2	1.244(1.033~1.499)	Ref.	1.196(0.993~1.440)	1.131(0.935~1.368)
Model 3	1.243(1.032~1.498)	Ref.	1.211(1.005~1.459)	1.151(0.951~1.393)
Model 4	1.207(1.001~1.455)	Ref.	1.215(1.007~1.466)	1.203(0.989~1.462)
Model 5	1.249(1.036~1.505)	Ref.	1.209(1.003~1.458)	1.140(0.940~1.384)
RC-VIM	<0.417	0.417~0.636	0.636~0.849	≥0.849
Event/Total	243/9 824	216/9 825	232/9 825	225/9 825
Incidence density/1 000 person-years	3.391	2.954	3.145	3.069
Model 1	1.186(0.987~1.425)	Ref.	1.072(0.891~1.291)	1.045(0.867~1.260)
Model 2	1.186(0.987~1.424)	Ref.	1.080(0.898~1.301)	1.068(0.885~1.289)
Model 3	1.184(0.985~1.422)	Ref.	1.094(0.908~1.317)	1.088(0.900~1.314)
Model 4	1.143(0.951~1.374)	Ref.	1.097(0.910~1.323)	1.151(0.947~1.397)
Model 5	1.197(0.996~1.438)	Ref.	1.092(0.907~1.315)	1.076(0.889~1.302)

Model 1: adjusted for age and sex; Model 2: Adjusted for variables in model 1 and smoking, alcohol consumption, body mass index, and physical activity; Model 3: Adjusted for variables in model 2 and diabetes, hypertension, hyperlipemia, eGFR, hs-CRP, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs; Model 4: Adjusted for variables in model 3 and RC in 2010; Model 5: Adjusted for variables in model 3 and RC in 2006; RC: Remnant cholesterol; ARV: Average real variability; CV: Coefficient of variation; VIM: Variability independent of the mean; hs-CRP: High-sensitivity C-reactive protein; eGFR: Estimated glomerular filtration rate; Ref: reference; CCB: Cardiac conduction block; *HR*: hazard ratio; *CI*: confidence interval

2.4 敏感性分析

为保证结果的稳健性,以RC-SD为自变量,CCB及其亚型为因变量进行了敏感性分析:排除随访2年内即发生CCB的人群(n=38 644)。排除基线及随访时发生心衰及急性心肌梗死的人群(n=37 718)。排除使用降脂药的人群(n=37 537)。校正年龄、性别、吸烟、饮酒、体育锻炼、BMI、eGFR、高血压、糖尿病、高血脂、hs-CRP、打鼾、降压药、降糖药、降脂药、2010年的RC后,结果未发生显著变化。此外,使用Fine-Gray模型进行死亡竞争风险分析与主模型保持一致,见表4。

2.5 分层分析

本研究分别以年龄、性别、高血压、糖尿病为分层变量,将结局事件为CCB和AVB进行了分层分析,校正年龄、性别、吸烟、饮酒、体育锻炼、BMI、eGFR、高血压、糖尿病、高血脂、hs-CRP、打鼾、降压药、降糖药、降脂药、2010年的RC等混杂因素后,RC-SD与CCB的关联在年龄、性别、高血压、糖尿病中没有显著交互作用($P_{interaction}$>0.05),但在年龄≥55岁、男性、非高血压和非糖尿病患者中RC-SD与CCB的关联更显著,在AVB中得到了类似的结论,见表5。

表4 以RC-SD分组的残余胆固醇变异性与心脏传导阻滞及其亚型的敏感性分析

Table 4 Sensitive analysis for associations between variability of remnant cholesterol and risk of CCB and its subtypes stratified by RC-SD

Factors	n	*HR* (95% *CI*)			
		Q1	Q2	Q3	Q4
Cardiac conduction block					
Sensitivity analysis 1	38 644	1.339(1.103~1.627)	Ref.	1.057(0.865~1.290)	1.244(1.027~1.508)
Sensitivity analysis 2	37 718	1.315(1.081~1.598)	Ref.	1.054(0.863~1.287)	1.271(1.050~1.539)
Sensitivity analysis 3	37 537	1.316(1.083~1.599)	Ref.	1.028(0.841~1.257)	1.273(1.051~1.542)
Sensitivity analysis 4	39 299	1.344(1.110~1.626)	Ref.	1.068(0.878~1.299)	1.311(1.089~1.579)
Atrioventricular block					
Sensitivity analysis 1	38 675	1.640(1.142~2.357)	Ref.	1.606(1.127~2.288)	1.628(1.141~2.322)
Sensitivity analysis 2	37 718	1.689(1.170~2.438)	Ref.	1.711(1.199~2.441)	1.724(1.206~2.464)
Sensitivity analysis 3	37 537	1.731(1.198~2.502)	Ref.	1.686(1.175~2.421)	1.815(1.267~2.599)
Sensitivity analysis 4	39 299	1.354(1.119~1.639)	Ref.	1.077(0.886~1.309)	1.315(1.092~1.583)
Bundle branch block					
Sensitivity analysis 1	38 665	1.428(1.119~1.824)	1.195(0.935~1.528)	Ref.	1.160(0.907~1.482)
Sensitivity analysis 2	37 718	1.421(1.110~1.819)	1.231(0.962~1.575)	Ref.	1.221(0.956~1.560)
Sensitivity analysis 3	37 537	1.438(1.123~1.842)	1.255(0.981~1.606)	Ref.	1.223(0.955~1.565)
Sensitivity analysis 4	39 299	1.259(1.041~1.522)	0.935(0.769~1.137)	Ref.	1.224(1.020~1.468)
Right bundle branch block					
Sensitivity analysis 1	38 675	1.480(1.127~1.944)	1.140(0.862~1.506)	Ref.	1.063(0.801~1.412)
Sensitivity analysis 2	37 718	1.442(1.094~1.899)	1.147(0.867~1.519)	Ref.	1.131(0.854~1.498)
Sensitivity analysis 3	37 537	1.452(1.099~1.917)	1.201(0.907~1.589)	Ref.	1.134(0.852~1.509)
Sensitivity analysis 4	39 299	1.258(1.040~1.522)	0.932(0.766~1.133)	Ref.	1.221(1.018~1.466)
Left bundle branch block					
Sensitivity analysis 1	38 682	1.407(0.917~2.160)	1.352(0.882~2.073)	Ref.	1.198(0.781~1.837)
Sensitivity analysis 2	37 718	1.369(0.889~2.107)	1.375(0.899~2.104)	Ref.	1.207(0.787~1.852)
Sensitivity analysis 3	37 537	1.500(0.986~2.280)	1.344(0.882~2.050)	Ref.	1.186(0.776~1.813)
Sensitivity analysis 4	39 299	1.259(1.041~1.523)	0.931(0.766~1.133)	Ref.	1.220(1.017~1.464)

Sensitivity analysis 1: Excluding the individuals with new-onset cases within first 2 years of follow-up; Sensitivity analysis 2: Excluding the individuals who experienced myocardial infarction or heart failure during follow-up time; Sensitivity analysis 3: Excluding individuals who had ever used lipid-lowering medications; Sensitivity analysis 4: Competing risk regression to address mortality related confounding; Model: Adjusted for age, sex, smoking, alcohol consumption, body mass index, physical activity, diabetes, hypertension, hyperlipemia, eGFR, hs-CRP, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs, and RC in 2010. RC: Remnant cholesterol; SD: Standard deviation; hs-CRP: High-sensitivity C-reactive protein; eGFR: Estimated glomerular filtration rate; CCB: Cardiac conduction block; Ref: Reference; *HR*: Hazard ratio; *CI*: Confidence interval

表5 以RC-SD分组的残余胆固醇变异性与心脏传导阻滞及其亚型的分层分析

Table 5 Stratified analysis for associations between variability of remnant cholesterol and risk of CCB and its subtypes stratified by RC-SD

Factors	$P_{interaction}$	*HR* (95% *CI*)			
		Q1	Q2	Q3	Q4
Cardiac conduction block					
Age<55 years	0.37	1.330(1.007~1.755)	Ref.	0.954(0.719~1.266)	1.158(0.878~1.527)
Age≥55 years		1.351(1.037~1.759)	Ref.	1.208(0.921~1.584)	1.492(1.158~1.921)
Female	0.67	1.254(0.825~1.905)	Ref.	1.039(0.684~1.578)	1.229(0.829~1.822)
Male		1.370(1.105~1.698)	Ref.	1.081(0.866~1.348)	1.327(1.074~1.639)
Hypertension	0.65				
No		1.492(1.134~1.962)	Ref.	0.968(0.720~1.303)	1.411(1.077~1.850)
Yes		1.227(0.940~1.603)	Ref.	1.150(0.886~1.492)	1.229(0.952~1.587)
Diabetes	0.72				
No		1.348(1.101~1.652)	Ref.	1.084(0.880~1.334)	1.316(1.078~1.605)
Yes		1.273(0.725~2.237)	Ref.	0.952(0.535~1.696)	1.308(0.772~2.218)
Atrioventricular block					
Age<55 years	0.10	2.274(1.358~3.809)	Ref.	1.740(1.037~2.918)	1.698(0.995~2.897)
Age≥55 years		1.350(0.816~2.233)	Ref.	1.740(1.084~2.794)	1.969(1.244~3.115)
Female	0.07	1.781(0.855~3.712)	Ref.	1.153(0.531~2.505)	1.182(0.550~2.542)
Male		1.710(1.133~2.579)	Ref.	1.930(1.303~2.858)	2.018(1.365~2.984)
Hypertension	0.61				
No		1.825(1.122~2.969)	Ref.	1.060(0.621~1.810)	2.013(1.256~3.229)
Yes		1.593(0.935~2.712)	Ref.	2.437(1.510~3.933)	1.581(0.948~2.636)
Diabetes	0.80				
No		1.692(1.162~2.465)	Ref.	1.597(1.105~2.309)	1.707(1.184~2.461)
Yes		2.167(0.641~7.330)	Ref.	3.474(1.098~10.994)	3.467(1.093~10.994)

Model: Adjusted for age, sex, smoking, alcohol consumption, body mass index, physical activity, diabetes, hypertension, hyperlipemia, eGFR, hs-CRP, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs, and RC in 2010. RC: Remnant cholesterol; SD: Standard deviation; hs-CRP: High-sensitivity C-reactive protein; eGFR: Estimated glomerular filtration rate; CCB: Cardiac conduction block; Ref: Reference; *HR*: Hazard ratio; *CI*: Confidence interval

3 讨论

在这项基于开滦研究的大型队列研究中,本研究发现RC的变异性与CCB的发生风险呈U型关联,即较高或较低的RC变异性均与CCB的发生风险增加相关,这种关联呈现出传导部位依赖。RC的变异性与CCB的关联受年龄、性别、是否患高血压、糖尿病影响,且独立于单次测量值。

本研究发现,RC的变异性与CCB的发生风险呈U型关联。高RC的变异性使CCB的发生风险增加31%,使AVB的发生风险增加80%。这与既往研究类似,即较高的RC变异性能够促进心律失常及心脑血管事件的发生。ARIC研究显示,较高的RC变异性使房颤的发生风险增加30%[9]。ACCORD研究发现高RC变异性使MACE的发生风险增加约40%[10]。既往开滦研究表明,RC的变异性每增加一个标准差,缺血性卒中的风险增加9%[19]。此外,本研究发现,低RC变异性使CCB发生风险增加34%,使AVB的发生风险增加72%。目前,尚无研究发现RC变异性较低与心血管疾病的发生风险增加有关。本研究观察到这一结果,可能与本研究RC变异性水平较低者,RC的绝对水平也相对较低有关。这与既往研究类似,即较低的RC也能促进心血管事件的发生,CHEN等[20]对392 783名观察对象进行为期12.8年的随访发现,较低的RC水平使房颤的发生风险增加40%。一项来自UKB数据库的研究发现RC升高使房颤风险降低15%[21]。NHANES数据研究表明,RC与全因死亡呈U型关联[22]。ZHAO等[23]也发现高RC水平使心衰患者死亡

风险降低41%。可能的机制如下:低RC变异性意味着RC水平波动较小,RC是细胞膜胆固醇的重要来源,长期低RC水平可能使细胞膜胆固醇含量减少,从而改变磷脂双层的流动性,影响心肌细胞膜的稳定性和离子通道功能,进而损害心肌细胞的正常电活动,最终增加CCB的发生风险[24]。因此,在临床和公共卫生实践中,不仅应关注RC的绝对水平,也应重视其动态变化,过度追求RC水平的长期稳定可能并非最优策略,适度的生理波动或许对维持心脏电活动的稳定性至关重要。

RC的变异性与CCB的关联呈现部位依赖。其中,与AVB的关联最明显,与RBBB的关联性较差,在LBBB中未发现关联。较低的RC变异性分别使AVB和RBBB的风险增加72%和44%,较高的RC变异性分别使AVB和RBBB的风险增加80%和13%。在LBBB中未发现这种关联,可能是因为发生LBBB的人数较少。RC变异性与AVB的关联性较强可能与解剖结构和代谢差异有关。既往开滦研究也发现类似的结果,即BMI与AVB的关联优于其他CCB亚型[25],LI等[26]发现尿酸与hs-CRP对AVB的联合关联优于其他CCB亚型,RC的变异性可能提示代谢紊乱的持续存在,进而加重全身低度炎症反应,诱导心肌细胞的氧化应激,进而影响房室结的传导功能[27-28]。相比之下,束支传导系统对炎症反应的耐受性较高,受炎症反应的影响较小[29],未来的研究还需进一步明确RC变异性与心脏传导部位的分子机制,为心脏传导系统疾病的预防提供新的思路。

RC的变异性与CCB的关联独立于单次测量值。在分别校正2006年和2010年的RC后,结果无显著变化,提示RC的变异性可能是一项独立的危险因素,这与既往研究类似。BHMC研究表明,RC的变异性与动脉粥样硬化的风险升高相关,且独立于LDL-C[30]。基线RC仅代表某一特定时间的RC水平,容易受多种混杂因素的影响,例如饮食、药物、体质量变化等,而RC的变异性反映了其波动情况,能够很好地消除短期干扰因素的影响,更好地反映RC代谢状态对心血管疾病的影响[31]。因此,未来的研究不仅应着眼于降低RC水平,更应该关注其波动情况,加强对生活方式的干预,避免过快降脂,以防对血管造成额外损伤。

RC的变异性与CCB的关联在老年人群中更显著,之前的开滦研究也发现类似的结果,LIU等[25]对86 635名研究对象进行10.6年的随访,发现在老年人中,肥胖使CCB的风险增加44%。本研究发现RC的变异性与CCB的关联在男性患者中更为突出,这可能与雌激素作用相关,雌激素可以降低心肌纤维化的发生及增强心肌细胞的抗氧化能力[32-34],这可能抵消RC对CCB的影响。RC的变异性在高血压和糖尿病患者中与CCB发生风险的关联不明显,可能是因为高血压和糖尿病本身就是CCB的危险因素[35-36]。既往研究表明,高血压患者心血管会发生以动脉重塑、心肌纤维化为特征的结构及功能变化[37-38]。而对于糖尿病患者而言,高血糖和胰岛素抵抗会增加氧化应激,影响心肌细胞正常代谢,最终导致血管炎症和纤维化[39]。综上所述,RC变异性对CCB发生风险的影响存在人群差异,在年龄≥55岁、男性、非高血压和非糖尿病患者中更为显著。未来的研究应进一步探讨其机制,并在心血管疾病防控中纳入个体化管理策略,以提高干预的针对性和效果。

综上所述,本研究基于大型前瞻性队列,探讨了RC的变异性与CCB的关联,并通过尽可能排除相关混杂因素,进行敏感性分析及分层分析以提高结果的可靠性。本研究也存在一定局限性:首先,本研究的RC是通过公式(RC=TC-HDL-C-LDL-C)计算的,而不是直接测量的,可能会对结果产生影响,建议未来研究采用直接测量方法(如超速离心或核磁共振)进行验证。其次,本研究仅使用4个变异性指标,未来需要考虑更多的变异性指标。尽管本研究对混杂因素进行了严格调整,但仍有可能出现残留混杂因素,需要进行随机对照试验来进一步调查所发现的关联。

基于上述发现,未来血脂管理的潜在策略可能是:将人群RC变异性长期稳定在"U型曲线底部"所对应的低-中等波动区间,避免过高和过低的极端波动,平稳降脂,防止对心血管系统造成额外损伤。

利益冲突 本文所有作者声明不存在利益冲突

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(**收稿**:2025-10-21;**修回**:2026-01-03)

(编辑 邓强庭)