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摘要:目的 探讨术后C反应蛋白水平与术后房颤发生情况的关系。**方法** 回顾性分析我院2018年9月~2021年5月期间进行体外循环手术的550例患者,根据排除标准进行研究对象的筛选,最终入选患者363例,采用非参数检验(两独立样本Wilcoxon秩和检验)对年龄、术后早期C反应蛋白与术后房颤发生情况进行单因素分析,采用χ^2检验分析研究对象性别、疾病类型、合并症发生情况与术后房颤发生情况的关系;多因素分析采用二分类logistic回归。**结果** 本次研究中共入组363例患者,其中瓣膜病247例,主动脉夹层42例,冠心病37例,先天性心脏病37例。术后房颤发生人数101人,发生率为27.82%;术后C反应蛋白中位数88.65 mg/L,年龄中位数为57岁,最小5岁,最大77岁;将研究对象根据术后心房颤动的发生分为房颤组和窦性组。使用单因素和多因素相关性研究显示,术后早期C反应蛋白是术后心房颤动发生的重要因素。**结论** 术后早期升高的C反应蛋白与术后房颤的发生有关系。
关键词:术后房颤;体外循环;心脏手术;C反应蛋白

Elevation of C-reactive protein early after cardiopulmonary bypass surgery is associated with occurrence of postoperative atrial fibrillation

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Abstract: Objective To explore the association between postoperative C-reactive protein (CRP) levels and the occurrence of postoperative atrial fibrillation in patients undergoing cardiopulmonary bypass surgery. **Methods** We retrospectively analyzed the data of 550 patients undergoing cardiopulmonary bypass surgery in our hospital from September, 2018 to May, 2021, and after screening against the exclusion criteria, 363 patients were selected for further analysis. Univariate analysis was used to analyze the correlation of age and early postoperative CRP level with the occurrence of postoperative atrial fibrillation, and Chi-square test was used to explore the correlation of gender, disease type, and comorbidity with postoperative atrial fibrillation followed by multivariate analysis of the data using a binary logistic regression model. **Results** The 363 patients enrolled in this study included 247 with valvular disease, 42 with aortic dissection, 37 with coronary heart disease, and 37 with congenital heart disease, with a median postoperative CRP level of 88.65 mg/L and a median age of 57 years (range 5-77 years). Postoperative atrial fibrillation occurred in 101 (27.82%) of the patients, who were subsequently divided into atrial fibrillation group and sinus group. Univariate and multivariate correlation analyses showed that early postoperative elevation of CRP level was an important factor contributing to the occurrence of postoperative atrial fibrillation. **Conclusion** Early postoperative elevation of CRP level is associated with the occurrence of atrial fibrillation following cardiopulmonary bypass surgery.
Keywords: postoperative atrial fibrillation; cardiopulmonary bypass; cardiac surgery; C-reactive protein

术后心房颤动是心脏体外循环术后常见的并发症之一,其发生率为13%~44%[1]。术后心房颤动的发生严重影响着患者并发症的发生及死亡率,心律失常会引起心功能的改变,影响患者术后的恢复;同时心房颤动的发生,若抗凝治疗不达标,由于血流动力学的改变,有导致血栓形成,血栓脱落引起脏器梗阻缺血,甚至导致脑卒中的风险,增加患者住院时间及费用,以及术后死亡率[2-5]。通过筛选术后房颤发生风险较高的患者进行预防性治疗,尽量减少术后不必要的药物使用和房颤相关并发症的发生,减少患者的住院时间及费用。

为了更好的寻找预测指标,我们有必要了解术后房颤的发生机制,目前POAF的具体机制尚未完全清楚,

一般认为是术中和术后多因素、多机制共同作用的结果,如炎性反应、氧化应激、交感神经激活、心房缺血等[6-8]。其中炎症反应是重要因素之一[9,10],炎症导致心脏传导系统紊乱,促进POAF的发生[11,12],抗生素的使用,能有效地减低术后房颤的发生[11]。C反应蛋白作为炎症反应的重要指标,目前研究显示,术前高C反应蛋白值与术后房颤的发生有关[13-15]。但术后早期C反应蛋白数值与术后房颤的发生目前仍有争议[16-18]。本文通过回顾我院体外循环术后患者C反应蛋白数值与术后房颤的发生,进一步探讨二者的规律及其相关性,达到早期预防及治疗,减少术后房颤相关并发症的发生,降低住院费用、时间。

1 资料和方法

1.1 一般资料

回顾分析我院2018年9月~2021年5月期间行体

外循环手术的550例患者。入选标准:所有行体外循环心脏手术的患者。排除标准:(1)术前为心房颤动的患者;(2)术前为心房颤动,术中同期行房颤射频消融的患者;(3)术后有严重感染(如肺部感染等)的患者;(4)术后早期死亡(术后3 d内)的患者;(5)术后早期未严格监测C反应蛋白数值的患者共入选研究对象363例。术后早期常规每日行心电图检查,根据患者术后心电图结果(是否心房颤动)将研究对象分成房颤组和窦性组。

1.2 质量控制

所有手术均有我科高级职称固定1~2人实施完成,手术流程按照标准同质化进行。术后心律监测:术后每天监测心电图检查,1周内获取房颤心律则有意义;C反应蛋白数值:术后每天监测C反应蛋白数值,具前期观察统计,患者一般术后3~4 dC反应蛋白数值达到顶峰,故本研究主要选取术后3~4 dC反应蛋白数值,若其余日期有更高的数值,则选取最高值。

1.3 统计学分析

统计学软件采用SPSS 21.0软件包,统计描述:首先对计量资料进行正态性检验,满足正态分布时采用均数±标准差,不满足正态分布时采用M(Q25,Q75),计数资料采用n(%)表示;统计推断:若计量资料满足正态性,单因素分析采用两独立样本t检验,若计量资料不满足正态性检验则采用非参数检验(两独立样本Wilcoxon秩和检验),计数资料的单因素分析采用χ检验。多因素分析采用二分类logistic回归分析。检验水准α=0.05。

2 结果

2.1 基本情况

本次研究中共入组363例患者,其中瓣膜病247例,主动脉夹层42例,冠心病37例,先天性心脏病37例。术后房颤101例,发生率为27.82%;术后C反应蛋白中位数88.65 mg/L,年龄中位数为57岁,最小5岁,最大77岁;术后早期每日行心电图检查,根据心电图结果将研究对象根据术后心房颤动的发生分为房颤组(AF)和窦性组。具体见表1。

2.1 术后房颤发生影响因素的单因素分析

研究对象房颤发生可能影响因素(性别、年龄、合并症、疾病类型、术后C反应蛋白)进行单因素分析(表2),患者术后发生心房颤动的可能影响因素中,年龄、疾病类型、术后C早期C反应蛋白数值具有统计学意义($P<0.05$),影响术后心房颤动的发生。

2.2 术后房颤发生影响因素的多因素分析

对研究对象房颤发生可能影响因素的多因素分析采用二元logistc回归分析,以术后房颤的发生与否为因变量(窦性心律=0,房颤=1),共纳入5个自变量(性别、

年龄、合并症、疾病类型、术后早期C反应蛋白),采用向后似然比进行自变量选择(表3)。术后房颤发生影响因素的多因素分析显示,疾病类型、术后早期C反应蛋白数值与术后心房颤动的发生有统计学意义($P<0.01$),疾病类型中,与主动脉夹层对照,瓣膜病术后心房颤动的发生具有统计学意义,影响术后心房颤动的发生。

3 讨论

心脏术后早期心房颤动是一个较常见的并发症,目前研究显示其诱发因素是多方面的,其中炎症反应是重要影响因素之一,而C反应蛋白作为炎症主要指标之一,之前的研究中显示,其与术后房颤的发生有一定关系。本研究通过回顾分析本中心的相关数据,旨在探讨C反应蛋白与术后早期心房颤动发生的关系。本研究中影响心房颤动术后发生的单因素分析显示,年龄、疾病类型、术后C早期C反应蛋白数值具有统计学意义,影响术后心房颤动的发生。既往研究显示,年龄是术后房颤发生的一大因素[19],随着年龄的增长,术后心房颤动发生的几率大大增高[20-23],Shen等[21]研究表明72岁及以上患者发生术后心房颤动的可能性是12~54岁患者的5.57倍。这可能与高龄患者耐受多年心脏疾病的困扰,心脏功能下降,心脏结构改变更严重。同时患者随着年龄增高,免疫功能逐步下降,术前合并症多,肺部情况差,术中耐受体外循环炎性反应的能力越差,术后早期合并感染及其他并发症的几率更大,炎症反应更重,C反应蛋白值更高等方面有关。疾病类型影响着术后心房颤动的发生,本研究结果显示,疾病类型也是影响着患者术后心房颤动的发生率的因素之一,其中瓣膜病术后心房颤动发生率远远高于其他心脏疾病,如冠心病、大血管疾病、先天性心脏病等,这主要与瓣膜病更容易导致心脏结构的改变有关,从而引起心脏重塑,引起术后心房颤动的发生。

炎症反应是术后心房颤动发生的主要机制之一[10,24],但其具体机制仍不清楚,目前相关研究验证了炎症与术后早期心房颤动发生的相关性。Ishiid等[25]研究表明导致AF的折返回路取决于炎症的程度,并且发生在炎症最严重、传导不均匀和心房切开的区域。炎症是一个复杂的过程,参与释放细胞因子或增加氧化应激。促炎细胞因子,如白介素或肿瘤坏死因子(TNF)-α,也影响术后心房颤动的发展。已经证明,白介素-6或TNF-α降低肌细胞中的钙电流,导致动作电位持续时间和不应期的缩短,并通过多回路再入诱导和维持心房颤动。炎症介质通过改变电活动,从而改变体外循环后白细胞介素(ILs)和CRP的释放,从而导致导致一氧化氮的释放受损,进而引起术后心房颤动的发生[26-30]。Tselentakis等[11]通过动物实验分析花生四烯酸诱导的急性炎症减慢了

表1　研究对象基本情况

Tab.1　Demographic and clinical data of the patients experiencing preoperative atrial fibrillation

Variable	Total patient count	AF group	Sinus group
Age (year)	57 (50, 65)	64 (56, 68)	55 (47, 65)
Gender			
Male	193 (53.2%)	76 (75.2%)	117 (44.7%)
Female	170 (46.8%)	25 (24.8%)	145 (55.3%)
Comorbidity			
Yes	187 (51.5%)	70 (59.4%)	127 (48.5%)
No	176 (48.5%)	41 (40.6%)	135 (51.5%)
Disease type			
Valve disease	247 (68.0%)	73 (72.2%)	174 (66.4%)
Aortic dissection	42 (11.6%)	13 (12.9%)	29 (11.1%)
Coronary heart disease	37 (10.2%)	13 (12.9%)	24 (9.2%)
Congenital heart disease	37 (10.2%)	2 (2.0%)	35 (13.3%)
C-reactive protein	88.65 (65.45, 111.23)	167.54 (116.93, 200.88)	77.52 (57.53, 91.54)

表2　术后房颤发生影响因素的单因素分析

Tab.2　Univariate analysis of factors associated with postoperative atrial fibrillation

Variable	AF group	Sinus group	Testing Statistic	P
Age (year)	64 (56, 68)	55 (47, 65)		<0.01
Gender			27.40	<0.01
Male	76 (75.2%)	117 (44.7%)		
Female	25 (24.8%)	145 (55.3%)		
Comorbidity			3.49	0.06
Yes	70 (59.4%)	127 (48.5%)		
No	41 (40.6%)	135 (51.5%)		
Disease type			11.24	0.01
Valve disease	73 (72.2%)	174 (66.4%)		
Aortic dissection	13 (12.9%)	29 (11.1%)		
Coronary heart disease	13 (12.9%)	24 (9.2%)		
Congenital heart disease	2 (2.0%)	35 (13.3%)		
C-reactive protein	167.54 (116.93, 200.88)	77.52 (57.53, 91.54)		<0.01

传导速度,这可能为心房再入奠定基础,同时抗炎药物的使用降低了持续性房颤的发生率,表明炎症在POAF的发展中发挥了重要作用。C反应蛋白是应用广泛的炎性预测指标,也是体外循环术后房颤发生的独立预测因子[2, 31],同时最近发表的一些meta分析也提示同样的结论[16, 22, 33, 34]。本文统计了我院近年来体外患者的相关临床数据,以术后心律为分组变量,首先通过单因素分析,显示C反应蛋白是术后早期心房颤动发生的关系。为进一步排除其他因素的干扰,再将所有数据进行影响术后心房颤动发生的多因素分析,结果显示C反应蛋白是术后心房颤动发生的明显影响因素。综合来看,患者

术后早期C反应蛋白数值影响着术后心房颤动的发生,同时是正向关系,二元logistc回归分析显示其OR值为1.05,表示术后C反应蛋白值严重影响着术后心房颤动的发生,C反应蛋白值越高,术后心房颤动的发生率越高。

本文主要通过回顾分析本中心近年病例的相关资料,研究探讨了可能影响术后早期心房颤动发生的一些影响因素。研究数据结果显示,年龄、术后早期C反应蛋白数值增高、疾病类型是术后早期心房颤动发生的重要影响因素。这一研究对我们临床工作有重要的指导意义,在临床中,收治老年心脏手术患者,特别是心脏瓣

表3　术后房颤发生影响因素的多因素分析
Tab.3　Multivariate analysis of the factors associated with postoperative atrial fibrillation

Factor	β	Wald	OR	OR95% *CI*	*P*
Gender	0.44	1.46	1.55	(0.76-3.17)	0.86
Age (year)	0.03	1.75	1.23	(0.99-1.07)	0.19
C-reactive protein	0.04	81.46	1.05	(1.04-1.06)	<0.01
Disease type		10.79			0.02
Valve disease(*vs* AD)	1.76	7.90	5.79	(1.70-19.70)	<0.01
Coronary heart disease (*vs* AD)	0.22	0.03	1.25	(0.12-12.50)	0.85
Congenital heart disease (*vs* AD)	0.55	0.43	1.73	(0.33-9.08)	0.51
Comorbidity	0.06	0.03	1.07	(0.50-2.29)	0.86

AD: Aortic dissection.

膜疾病时,我们需更多的关注患者术后早期炎性标志物,特别是C反应蛋白数值的情况,有效的使用药物控制炎症的发生发生,从而降低术后心房颤动的发生;从而降低心脏血管并发症的的发生,减少住院时间及费用;更好地提高高龄患者的术后管理效率,提高临床效率。本文仅从临床统计数据中分析了这一结论,未来研究中可通过动物实验进一步验证探究这一结果,同时进一步探究其发生机制。

参考文献：

［1］ Perrier S, Meyer N, Hoang Minh T, et al. Predictors of atrial fibrillation after coronary artery bypass grafting: a Bayesian analysis［J］. Ann Thorac Surg, 2017, 103(1): 92-7.

［2］ Lahtinen J, Biancari F, Salmela E, et al. Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery［J］. Ann Thorac Surg, 2004, 77(4): 1241-4.

［3］ Omer S, Cornwell LD, Bakshi A, et al. Incidence, predictors, and impact of postoperative atrial fibrillation after coronary artery bypass grafting in military veterans［J］. Tex Heart Inst J, 2016, 43(5): 397-403.

［4］ LaPar DJ, Speir AM, Crosby IK, et al. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs［J］. Ann Thorac Surg, 2014, 98(2): 527-33.

［5］ Lin MH, Kamel H, Singer DE, et al. Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality［J］. Stroke, 2019, 50(6): 1364-71.

［6］ Thorén E, Hellgren L, Ståhle E. High incidence of atrial fibrillation after coronary surgery［J］. Interact CardioVasc Thorac Surg, 2016, 22(2): 176-80.

［7］ Butt JH, Xian Y, Peterson ED, et al. Long-term thromboembolic risk in patients with postoperative atrial fibrillation after coronary artery bypass graft surgery and patients with nonvalvular atrial fibrillation［J］. JAMA Cardiol, 2018, 3(5): 417.

［8］ Rezaei Y, Peighambari MM, Naghshbandi S, et al. Postoperative atrial fibrillation following cardiac surgery: from pathogenesis to potential therapies［J］. Am J Cardiovasc Drugs, 2020, 20(1): 19-49.

［9］ Dobrev D, Aguilar M, Heijman J, et al. Postoperative atrial fibrillation: mechanisms, manifestations and management［J］. Nat Rev Cardiol, 2019, 16(7): 417-36.

［10］ Rezaei Y. Anti-inflammatory role of statins in preventing postoperative atrial fibrillation［J］. Am J Cardiol, 2016, 117(2): 314.

［11］ Tselentakis EV, Woodford E, Chandy J, et al. Inflammation effects on the electrical properties of atrial tissue and inducibility of postoperative atrial fibrillation［J］. J Surg Res, 2006, 135(1): 68-75.

［12］ Zakkar M, Ascione R, James AF, et al. Inflammation, oxidative stress and postoperative atrial fibrillation in cardiac surgery［J］. Pharmacol Ther, 2015, 154: 13-20.

［13］ Ishida K, Kimura F, Imamaki M, et al. Relation of inflammatory cytokines to atrial fibrillation after off-pump coronary artery bypass grafting［J］. Eur J Cardio Thorac Surg, 2006, 29(4): 501-5.

［14］ Wu N, Xu B, Xiang Y, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis［J］. Int J Cardiol, 2013, 169(1): 62-72.

［15］ Balciunas M, Bagdonaite L, Samalavicius R, et al. Pre-operative high sensitive C-reactive protein predicts cardiovascular events after coronary artery bypass grafting surgery: a prospective observational study［J］. Ann Card Anaesth, 2009, 12(2): 127.

［16］ Weymann A, Popov AF, Sabashnikov A, et al. Baseline and postoperative levels of C-reactive protein and interleukins as inflammatory predictors of atrial fibrillation following cardiac surgery: a systematic review and meta-analysis［J］. Kardiol Pol, 2018, 76(2): 440-51.

［17］ Anatoĺevna RO, Veniaminovich FO, Mikhaylovich KS. Predictors of new-onset atrial fibrillation in elderly patients with coronary artery disease after coronary artery bypass graft［J］. J Geriatr Cardiol, 2016, 13(5): 444-9.

［18］ Pilatis ND, Anyfantakis ZA, Spiliopoulos K, et al. The role of BNP and CRP in predicting the development of atrial fibrillation in patients undergoing isolated coronary artery bypass surgery［J］. ISRN Cardiol, 2013, 2013: 1-6.

［19］ Gudbjartsson T, Helgadottir S, Sigurdsson MI, et al. New-onset postoperative atrial fibrillation after heart surgery［J］. Acta Anaesthesiol Scand, 2020, 64(2): 145-55.

［20］ Mathew JP. A multicenter risk index for atrial fibrillation after cardiac surgery［J］. JAMA, 2004, 291(14): 1720.

［21］ Shen J, Lall S, Zheng V, et al. The persistent problem of new-onset

postoperative atrial fibrillation: a single-institution experience over two decades[J]. J Thorac Cardiovasc Surg, 2011, 141(2): 559-70.

[22] Baeza-Herrera LA, Rojas-Velasco G, Márquez-Murillo MF, et al. Atrial fibrillation in cardiac surgery[J]. Arch Cardiol Mex, 2019, 89 (4): 348-59.

[23] Mauro MD, Calafiore AM, di Franco A, et al. Association between cardioplegia and postoperative atrial fibrillation in coronary surgery [J]. Int J Cardiol, 2021, 324(1): 38-43.

[24] Abdelhadi RH, Gurm HS, van Wagoner DR, et al. Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively[J]. Am J Cardiol, 2004, 93(9): 1176-8.

[25] Ishii Y, Schuessler RB, Gaynor SL, et al. Postoperative atrial fibrillation: the role of the inflammatory response [J]. J Thorac Cardiovasc Surg, 2017, 153(6): 1357-65.

[26] Dehghani MR, Kasianzadeh M, Rezaei Y, et al. Atorvastatin reduces the incidence of postoperative atrial fibrillation in statin-naive patients undergoing isolated heart valve surgery[J]. J Cardiovasc Pharmacol Ther, 2015, 20(5): 465-72.

[27] Elahi MM, Flatman S, Matata BM. Tracing the origins of postoperative atrial fibrillation: the concept of oxidative stress-mediated myocardial injury phenomenon[J]. Eur J Cardiovasc Prev Rehabilitation, 2008, 15(6): 735-41.

[28] Siebert J, Lewicki Ł, Młodnicki M, et al. Atrial fibrillation after conventional and off-pump coronary artery bypass grafting: two

opposite trends in timing of atrial fibrillation occurrence?[J]. Med Sci Monit, 2003, 9(3): CR137-41.

[29] Turk T, Vural H, Eris C, et al. Atrial fibrillation after off-pump coronary artery surgery: a prospective, matched study[J]. J Int Med Res, 2007, 35(1): 134-42.

[30] Ucar H, Tok M, Atalar E, et al. Predictive significance of plasma levels of interleukin-6 and high-sensitivity C-reactive protein in atrial fibrillation after coronary artery bypass surgery[J]. Heart Surg Forum, 2007, 10(2): E131-5.

[31] Kubilay Karabacak, Emre Kubat, Furkan Burak Akyol, et al. The C-reactive protein/albumin ratio as a new predictor for postoperative atrial fibrillation after coronary artery bypass graft surgery[J]. J Card Surg, 2020, 35(10): 2747-53.

[32] Xie JYY, Noeman M, Pimenta D, et al. C-reactive protein as a predictor for developing post-operative atrial fibrillation[J]. EP Eur, 2021, 23(1): 159.

[33] Şaşkın H, Düzyol Ç, Aksoy R, et al. Do preoperative C-reactive protein and mean platelet volume levels predict development of postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting?[J]. Pwki, 2016, 2: 156-63.

[34] Seo C, Michie C, Hibbert B, et al. Systematic review of pre-clinical therapies for post-operative atrial fibrillation[J]. PLoS One, 2020, 15 (11): e0241643.

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