Heart & Lung 48 (2019) 515–518

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

The association of preoperative atrial fibrillation with post-cardiopulmonary bypass hyperfibrinolysis in rheumatic valvular heart disease patients

Zheng Guan [a], Yong-Jian Zhang [b], Lin Liu [a], Xin Shen [a], Yan-Feng Gao [a], Xiao-Gang Li [a], Rong-Sheng Zhou [a], Jing-Jie Liu [c,*]

[a] Department of Anesthesiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, PR China
[b] Department of Cardiac Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, PR China
[c] Department of Neurology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, PR China

ARTICLE INFO

Article history:
Received 24 December 2018
Received in revised form 22 March 2019
Accepted 18 May 2019
Available online 27 May 2019

Keywords:
Hyperfibrinolysis
Atrial fibrillation
Rheumatic valvular heart disease
Cardiopulmonary bypass

ABSTRACT

Objective: The purpose of this study was to assess the fibrinolytic status after cardiopulmonary bypass in rheumatic valvular heart disease patients, and detect the associated factors of post-cardiopulmonary bypass hyperfibrinolysis.
Methods: According to the fibrinolytic status after cardiopulmonary bypass, 203 rheumatic valvular heart disease patients were divided into two groups: hyperfibrinolysis group (H group, $n = 78$) and non-hyperfibrinolysis group (NH group, $n = 125$). The demographic characteristics, operative variables, and postoperative follow-ups were compared between these two groups.
Results: The incidence of hyperfibrinolysis was 38.4% after cardiopulmonary bypass. Patients in the H group had a significant higher incidence of preoperative atrial fibrillation than patients in the NH group (92.3% *vs.* 55.2%, $P < 0.01$). Furthermore, postoperative daily drainage (655.3 ± 131.5 ml *vs.* 535.4 ± 161.4 ml, $P < 0.01$), transfusion volume of fresh frozen plasma (621.8 ± 220.2 ml *vs.* 455.2 ± 208.5 ml, $P < 0.01$), and red blood cells (5.9 ± 2.2 u *vs.* 4.7 ± 2.8 u, $P < 0.01$) was greater in the H group than in the NH group. Moreover, the logistic regression analysis revealed that preoperative atrial fibrillation was associated with post-cardiopulmonary bypass hyperfibrinolysis (OR = 19.691, 95% CI = 6.849–56.612; $P < 0.05$).
Conclusion: Preoperative artial fibrillation is associated with post-cardiopulmonary bypass hyperfibrinolysis in rheumatic valvular heart disease patients.

Introduction

Rheumatic heart disease (RHD) is a leading non-communicable disease in low and middle income countries, and attributes to up to 1.4 million deaths per year.[1] Furthermore, RHD is the second cause of valvular heart disease (VHD) in European countries,[2] and is also the leading etiology of VHD in southern China.[3] To date, cardiac valvular surgery is the main treatment option for rheumatic VHD in China.[3]

Postoperative bleeding is a major complication after cardiac surgery, leading to increased morbidity and mortality.[4] Fibrinolysis activation plays an important role in post-cardiac surgery coagulopathy and bleeding.[5] However, it is difficult to predict postoperative hyperfibrinolysis due to individual variability.[6] Hence, it is significant to explore the associated factors of hyperfibrinolysis after cardiac valvular surgery in rheumatic VHD patients.

Thromboelastography (TEG) is a reliable, rapid and predictive point-of-care coagulation testing method, which measures the mechanical properties of the development of clots, maximum clot strength, and clot lysis.[7] A TEG-based diagnostic and therapeutic approach can significantly reduce postoperative bleeding in adult cardiac surgery,[8] and reduce morbidity in patients with bleeding.[9]

In the present study, the fibrinolytic status was detected by TEG in rheumatic VHD patients who underwent cardiac valvular surgery, in order to explore the associated factors of hyperfibrinolysis after cardiac valvular surgery in rheumatic VHD patients.

Materials and methods

The present study was a retrospective study. After obtaining the approval of the Local Ethics Committee, 203 rheumatic VHD patients were enrolled from January 2014 to December 2016. Data were collected from medical record, cardiopulmonary bypass (CPB) record, anesthesia record, and TEG record through hospital information system by our research team.

* Corresponding author.
E-mail address: drliujingjie@163.com (J.-J. Liu).

https://doi.org/10.1016/j.hrtlng.2019.05.014
0147-9563/$ - see front matter © 2019 Elsevier Inc. All rights reserved.

Inclusion criteria: patients who were ≥ 18 years old, had rheumatic VHD, patients underwent median sternotomy surgery, and received cardiac valvular surgery with CPB. Exclusion criteria: patients who had a reoperation, an emergency operation, renal or liver dysfunction, preoperative coagulation dysfunction, preoperative thrombocytopenia, and preoperative stroke.

Anesthesia was induced with 0.1 mg/kg of midazolam, 1–2 μg/kg of sufentanil, 0.1–0.3 mg/kg of etomidate, and 0.1 mg/kg of vecuronium, and anesthesia was maintained with 4–6 mg/kg h of propofol and 0.1–0.3 μg/kg min of remifentanil. In addition, vecuronium was intermittently injected at a dosage of 0.03 mg/kg.

CPB and cardiac arrest were performed for all the patients. Body temperature maintained at approximate 30 °C during cardiac arrest. Heparin was used at a dosage of 400 u/kg to maintain an activated coagulation time (ACT) of > 480 s during CPB. Protamine was used at a dosage of 3 mg/kg to reverse the heparin anticoagulation after patients were weaned from CPB. Antifibrinolytic agents, fresh frozen plasma (FFP) and coagulant drugs were not used before fibrinolytic status detection after CPB.

Venous blood samples were drawn, and the fibrinolytic status was detected after anesthesia induction (pre-CPB, T_1) and immediately after protamine infusion (post-CPB, T_2). The fibrinolytic status was detected by TEG after kaolin activation at T_1, and by TEG after kaolin activation in cups with heparinase at T_2. TEG parameters include the following: reaction time (R time), from the time blood was placed in the analyzer to initial fibrin formation; α angle and k value, the rapidity of the fibrin build-up; maximum amplitude (MA), the maximum dynamic properties of platelet and fibrin bonding; LY-30: clot lysis at 30 min after maximum clot strength. Hyperfibrinolysis was defined as an LY-30 of ≥7.5%.[10]

Statistical analysis

Continuous variables were described as mean ± standard deviation, while categorical variables were described as a number and in percentage. The statistical analysis was performed using the SPSS version 19.0 statistical software (SPSS Inc., Chicago, IL, USA). The statistical significance between groups was determined using independent-samples *t*-test for continuous variables and chi-square test for categorical variables. The statistical significance between T_1 and T_2 within groups was determined using one-way analysis of variance (ANOVA). Logistic regression analysis was used to identify the associated factors of hyperfibrinolysis after cardiac valvular surgery in rheumatic VHD patients. The statistical significance level was fixed at $P < 0.05$ and confidence interval was set at 95%.

Results

From January 2014 to December 2016, a total of 203 patients were eligible for inclusion into the present study, all the data were included in our study. According to fibrinolytic status at T_2, these patients were divided into two groups: hyperfibrinolysis group (H group, $n = 78$) and non-hyperfibrinolysis group (NH group, $n = 125$). The occurrence rate of hyperfibrinolysis after CPB was 38.4% in the present study. The enrollment chart was presented in Fig. 1.

The demographic characteristics of these patients are listed in Table 1. Preoperative atrial fibrillation (AF) incidence was significant higher in the H group than in the NH group (92.3% *vs.* 55.2%, $P<0.01$), but there were no significant differences in the other demographic characteristics between these two groups.

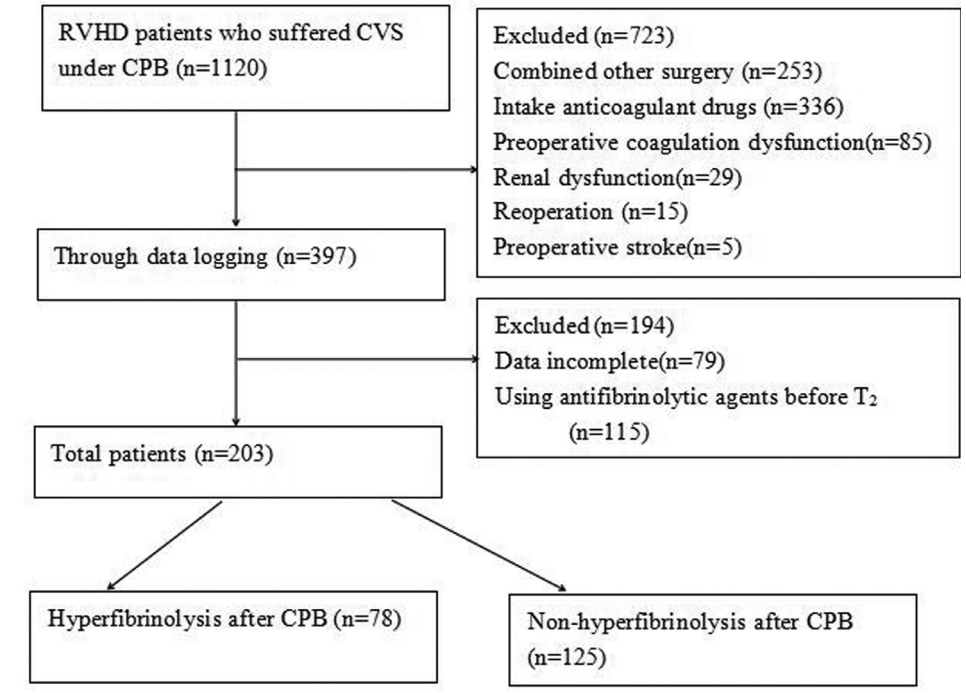

Fig. 1. The patients' enrollment chart.

Table 1
Clinical and demographic characteristics of the sample

	H group (n = 78)	NH group (n = 125)	P value
Male (n)(%)	23/(29.5%)	37/(29.6%)	0.553
Age (year)	54.2 ± 8.6	54.4 ± 8.5	0.865
BMI (kg/m^2)	22.9 ± 4.2	23.7 ± 4.6	0.228
NYHA(Ⅰ,Ⅱ/Ⅲ,Ⅳ)(n)	26/52	39/86	0.759
Hypertension (n)(%)	24(30.8%)	27(21.6%)	0.183
Diabetes (n)(%)	14(17.9%)	19(15.2%)	0.696
Atrial fibrillation (n)(%)	72(92.3%)	69(55.2%)	<0.01
Mitral stenosis (n)(%)	57 (73.1%)	94 (75.2%)	0.744

Data are presented as mean ± SD or number/percentage. BMI, body mass index; NYHA, New York heart association.

The operative variables are listed in Table 2. There were no significant differences in operative variables between the two groups.

ACT, R time, α angle, K value, MA and LY-30 were detected at T_1 and T_2 (Table 3). At T_1, there were no significant differences in ACT, R time, α angle, K value, MA and LY-30 between these two groups. At T_2, R time was significant shorter in the H group than in the NH group, LY-30 was significantly larger in the H group than in the NH group, but there were no significant differences in ACT, α angle, K value and MA between these two groups. Furthermore, R time was significant shorter, LY-30 was significant larger at T_2 than at T_1 in the H group, but there was no significant difference when compared with the NH group. Moreover, the α angle and MA significantly decreased, while the K value was significantly prolonged at T_2, when compared with T_1, in both groups.

The details for the postoperative followed-up are presented in Table 4. Postoperative daily drainage, the transfusion of FFP and red blood cell (RBC) count were greater in the H group than in the NH group. However, there were no significant differences in the length of intensive care unit (ICU) stay, length of hospital stay, re-explore surgery and postoperative day-30 mortality between these two groups.

Logistic regression analysis was performed to examine the variables that best predict hyperfibrinolysis. Gender, age, body mass index (BMI), hypertension, diabetes, AF, aortic clamp time, CPB time, operation time, the lowest temperature, and HCT during CPB were used as covariates. It was found that preoperative AF was associated with post operative hyperfibrinolysis (OR = 19.691, 95% CI = 6.849–56.612; $P < 0.05$).

Discussion

In the present study, the occurrence of hyperfibrinolysis after CPB in rheumatic VHD patients was 38.4%, and preoperative AF was associated with post-CPB hyperfibrinolysis. CPB activates the kallikrein–kinin system, which can cause the endogenous bradykinin concentration to increase. This in turn stimulates the release of tissue-type plasminogen activator (t-PA),[11] which can cause plasminogen activation and fibrinolysis.[12] In addition, CPB can activate inflammatory response, which is interconnected with coagulation-fibrinolytic cascades.[13] Previous studies have shown that the D-dimer[5,14] and t-PA concentration[14] immediately increased after on-pump coronary artery bypass grafting (CABG) surgery. In children, fibrinolysis occurs during CPB and at up to six hours after cardiac surgery.[15] Hyperfibrinolysis is known to occur during and after CPB, but in approximately one-third of patients, there will be no change in t-PA concentration after CPB.[6]

The incidence of AF is 21.8% in RHD patients,[1] and AF patients experience a hypercoagulable status. A meta-analysis revealed that coagulation markers, such as fibrinogen, prothrombin fragment 1–2, and the thrombin-antithrombin (TAT) complex, were significantly higher in AF patients than in sinus rhythm patients,[16] and that plasma antithrombin levels were significantly reduced in paroxysmal AF patients.[17] Hence, the fibrinolytic status of AF patients remains controversial. Furthermore, a meta-analysis revealed that fibrinolytic markers, such as t-PA, fibrinopeptide-A and D-dimer, were significantly higher in AF patients than in sinus rhythm patients.[16] Moreover, other studies revealed that the plasminogen activator inhibitor[16,18] was elevated, but t-PA was not elevated, in AF patients.[18] Using the global fibrinolytic capacity technique, another study revealed the hypofibrinolytic status of rheumatic AF patients.[19] AF patients usually underwent anticoagulant therapy, to eliminate the impact of oral anticoagulation, and patients who took anticoagulant drugs before operation were excluded. Aspirin and warfarin should be suspended 2 and 1 week before operation respectively. The result showed that R time was significant shorter at T_2 than at T_1 in the H group, and it was speculated that hyperfibrinolysis after CPB was secondary to hypercoagulability caused by AF.

Table 2
Operative variables of the patients

	H group (n = 78)	NH group (n = 125)	P value
Operation			
aortic valvular surgery (n)(%)	7(9%)	10(8%)	0.457
mitral valvular surgery (n)(%)	40(51.3%)	72(57.6%)	
combined valvular surgery (n)(%)	31(39.7%)	43(34.4%)	
Aortic clamp time (minute)	73.6 ± 22.5	74.2 ± 19.9	0.836
CPB time (minute)	109.9 ± 27.5	113.9 ± 26.2	0.297
Operation time (minute)	171.9 ± 39.4	169.5 ± 38.1	0.667
Lowest temperature (°C)	30.9 ± 1.6	30.7 ± 1.4	0.298
Lowest HCT (%)	21.3 ± 1.7	20.9 ± 2.1	0.155

Data are presented as mean ± SD or number/percentage. CPB, cardiopulmonary bypass; HCT, hematocrit.

Table 3
The haemostatic status before and after CPB which was monitored by TEG

	H group (n = 78)	NH group (n = 125)	P value
ACT			
T_1 (second)	113 ± 15.5	110.1 ± 12.1	0.162
T_2 (second)	112 ± 12.4	111.1 ± 10.9	0.598
R time			
T_1 (minute)	5.9 ± 1.2	6.1 ± 1.2	0.215
T_2 (minute)	5.3 ± 1.4*	5.9 ± 1.6	0.011
α angle			
T_1 (deg)	61.4 ± 5.6	62.3 ± 3.8	0.128
T_2 (deg)	56.1 ± 4.1*	57.2 ± 4.3*	0.095
K value			
T_1 (minute)	2.4 ± 0.5	2.5 ± 0.5	0.064
T_2 (minute)	3.4 ± 1.1*	3.4 ± 1.4*	0.974
MA			
T_1 (mm)	57.4 ± 4.6	56 ± 5.8	0.063
T_2 (mm)	45.2 ± 9.4*	45.4 ± 8.9*	0.834
LY-30			
T_1 (%)	5.8 ± 0.9	5.5 ± 1.3	0.058
T_2 (%)	9.1 ± 1.3*	5.6 ± 1.2	<0.001

Data are presented as mean ± SD. CPB, cardiopulmonary bypass; TEG, thromboelastography; ACT, activated coagulation time.
* compare to T_1, $P < 0.05$.

Table 4
The postoperative follow-ups

	H group (n = 78)	NH group (n = 125)	P value
Postoperative day drainage (ml)	655.3 ± 131.5	535.4 ± 161.4	<0.01
Transfusion			
RBC (unit)	5.9 ± 2.2	4.7 ± 2.8	<0.01
FFP (ml)	621.8 ± 220.2	455.2 ± 208.5	<0.01
ICU stay (hour)	29.7 ± 11	27.2 ± 12.4	0.144
Hospital stay (day)	9.9 ± 3.1	10.3 ± 3.2	0.398
Re-explore for bleeding (n)	2(2.6%)	5(4%)	0.71
30-d motality (n)	1(1.3%)	2(1.6%)	0.671

Data are presented as mean ± SD or number/percentage. RBC, red blood cell; FFP, fresh frozen plasma; ICU, intensive care unit.

Platelet activation and aggregation function was impaired after CPB, and the concentration of plasma coagulation factors also declined after CPB. Previous studies revealed that platelet count sharply fell after on-pump CABG surgery[14] and immediately after CPB in other cardiac surgeries.[5,7] Furthermore, the fibrinogen level also decreased after CPB.[14] In TEG parameters, MA indicates the platelet count and function, K value and α angle indicate the fibrinogen level. In the present study, MA decreased, the α angle was smaller, and the K value was significantly prolonged after CPB in all the patients, which were consistent with previous studies.

In the present study, postoperative chest tube drainage and FFP infusion requirement increased in hyperfibrinolysis patients. Hyperfibrinolysis was associated with increased bleeding and higher transfusion requirement in trauma patients.[20] Furthermore, chest tube drainage increased secondary to enhanced fibrinolysis after on-pump cardiac surgery,[21] and these were all consistent with the present study. Hyperfibrinolysis was an independent predictor of mortality in trauma patients,[22] and in patients with abdominal aortic aneurysm ruptures.[23] However, a previous study revealed that the predictors of mortality in cardiac valvular surgery for rheumatic VHD were complex.[24] Hence, there were no significant differences in 30-day mortality between hyperfibrinolysis and non-hyperfibrinolysis patients in the present study.

There were limitations in the present study. First, few biochemical makers were used to reflect the fibrinolysis, such as t-PA and the D-dimer, and LY-30 was used as the only judgment standard of hyperfibrionlysis in the present study. Second, the AF duration was not obtained in the present study. Third, the treatment history of AF was not obtained in the present study.

Conclusion

The incidence of hyperfibrinolysis after cardiac valvular surgery in rheumatic VHD patients is high. Preoperative AF is an associated factor of post-cardiac valvular surgery hyperfibrionlysis in rheumatic VHD patients.

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