Rapid thrombelastography predicts perioperative massive blood transfusion in patients undergoing coronary artery bypass grafting

A retrospective study

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Abstract

Massive blood transfusion (MBT) is a relatively common complication of cardiac surgery, which is independently associated with severe postoperative adverse events. However, the value of using rapid thrombelastography (r-TEG) to predict MBT in perioperative period of cardiac surgery has not been explored. This study aimed to identify the effect of r-TEG in predicting MBT for patients undergoing coronary artery bypass grafting (CABG).

This retrospective study included consecutive patients first time undergoing CABG at the Zhongnan Hospital of Wuhan University between March 2015 and November 2017. All the patients had done r-TEG tests before surgery. The MBT was defined as receiving at least 4 units of red blood cells intra-operatively and 5 units postoperatively (1 unit red blood cells from 200mL whole blood).

Lower preoperative hemoglobin level (P=0.001) and longer cardiopulmonary bypass time (P=0.001) were the independent risk factors for MBT during surgery, and no components of the r-TEG predicted MBT during surgery. Meanwhile, longer activated clotting time (P<0.001), less autologous blood transfusion (P=0.001), and older age (P=0.008) were the independent risk factors for MBT within 24 hours of surgery.

Preoperative r-TEG activated clotting time can predict the increase of postoperative MBT in patients undergoing CABG. We recommend the careful monitoring of coagulation system with r-TEG, which allows rapid diagnosis of coagulation abnormalities even before the start of surgery.

Abbreviations: ABT = autologous blood transfusion, ACT = activated clotting time, CABG = coronary artery bypass grafting, CAD = coronary atherosclerotic heart disease, CPB = cardiopulmonary bypass, Hb = hemoglobin, MA = maximum clot strength, MBT = massive blood transfusion, NYHA = New York Heart Association, RBC = red blood cells, r-TEG = rapid thrombelastography.

Keywords: coronary artery bypass grafting, massive blood transfusion, rapid thrombelastography.

1. Introduction

Massive blood loss resulting in multiple units of red blood cells (RBC) transfusion is a relatively common complication of cardiac surgery, which is independently associated with severe postoperative adverse events, such as sepsis, renal failure, acute respiratory distress syndrome, and death.[1-4] Predicting the probability of massive blood transfusion (MBT) in the perioperative period of cardiac surgery is of clinical and research significance. For example, it could limit the use of expensive blood preservation modalities in patients identified as being at low-risk for MBT, such as aprotinin or cell recovery and washing. It could also be used to develop preventive measures to reduce the risk of MBT in those identified as being at high-risk for MBT, such as modifying risk factors or prophylactic administration of coagulation factors or hemostatic agents.[5]

Previous studies have identified several risk factors associated with MBT in perioperative period of cardiac surgery, including female sex, older age, renal dysfunction, lower body mass index, lower preoperative hemoglobin (Hb) and longer cardiopulmonary bypass (CPB), which predicted MBT during cardiac surgery.[6] While body surface area, preoperative Hb concentration, preoperative platelet count, urgency of surgery, surgeon, and type of procedure predicted the MBT within 1 day after surgery.[3] However, the value of using rapid thrombelastography (r-TEG) to predict MBT in perioperative period of cardiac surgery has not been explored.

Compared with conventional coagulation tests, both r-TEG and conventional thrombelastographic (TEG) methods provided substantial time advantages in terms of data collection and interpretation. The r-TEG values are essentially the same as those
of conventional TEG; however, r-TEG uses tissue factor as activator of the coagulation process, and r-TEG activated clotting time (ACT) replaces the conventional TEG R time, which both reflect the function of soluble coagulation factors. The normal range of the R time in conventional TEG is between 2 and 8 minutes, whereas in r-TEG the normal range of ACT is 86 to 118 seconds. Therefore, the ability to more rapidly analyze critical data on coagulation state is a main advantage of using r-TEG over conventional TEG, especially in the emergency patients.

Since the introduction of r-TEG as a faster TEG method, numerous studies have examined its effectiveness in assessing the coagulation state of trauma patients, considering that r-TEG ACT was predictive of early transfusions. Nevertheless, no studies have reported predictive value of r-TEG for MBT in the perioperative phase of cardiac surgery. Consequently, we collected a variety of clinical and laboratory parameters associated with MBT, to identify the value of r-TEG in predicting MBT for patients undergoing coronary artery bypass grafting (CABG).

2. Methods

2.1. Patient population and data collection

This retrospective study included patients with coronary atherosclerotic heart disease who first time underwent CABG involving CPB at the Zhongnan Hospital of Wuhan University between March 2015 and November 2017. Patient data were collected from electronic medical records and were analyzed anonymously. The relevant ethics committees/institutional review boards approved this study, and informed consent was not required due to the retrospective study design.

We obtained the following perioperative data: demographics (age, sex, body mass index, history of smoking, and alcohol consumption), preoperative comorbidities (hypertension, diabetes, myocardial infarction, cerebral infarction, hepatic insufficiency, renal dysfunction, hyperlipemia, coronary stenting), heart function classification (New York Heart Association [NYHA] class, American Society of Anesthesiologists grade), history of medications (Angiotensin-Converting Enzyme Inhibitors/angiotensin II receptor blockers, β-adrenergic receptor blockers, calcium channel blockers, nitrates, antiplatelet drugs, anticoagulants, digitoxin, diuretics, lipid-regulating drugs), preoperative laboratory tests (cardiac ultrasonography, routine blood tests, blood biochemistry, coagulation examinations), surgical characteristics (emergency status, duration of operation, CPB duration, concomitant procedure, estimated intraoperative blood loss, autologous blood transfusion (ABT), fresh frozen plasma transfusion, platelet transfusion) and preoperative r-TEG values (ACT, K-time, angle, maximum amplitude). Intraoperative blood loss was estimated by the nurse anesthetist by counting wet swabs and drapes together with suction volume minus volume of any irrigation fluid used.

Inclusion criteria: consecutive patients scheduled for first time CABG were included in the study, who had done rapid thromboelastometry tests before surgery. Exclusion criteria: excluded from the study were patients scheduled for repeated cardiac surgery, patients with missing data that could not be obtained from hospital records, patients who had not had rapid thromboelastometry measurements done before surgery. Flow chart illustrating selection of the study group is presented in Figure 1.

2.2. Surgical procedures and definitions

All the patients were anesthetized, heparinized, undergoing CPB, and surgery was performed according to the existent standard protocol. Before induction of anesthesia and heparinization a sample of blood was removed from a peripheral artery for r-TEG tests. The adequacy of heparin anticoagulation during CPB was monitored by ACT (maintain ACT >480 seconds). At the
termination of CPB, heparin activity was reversed with protamine in a 1:1 ratio. Additional protamine was administered as needed until ACT returned to the baseline pre-heparin level. After surgery, patients were transferred to the intensive care unit.

In the present study, the definition for MBT during surgery was ≥4 units of RBC transfused. Because beyond this level of intraoperative blood transfusion was associated predominantly with significant increases in postoperative morbidity and mortality, \(^{11,12}\) the MBT within 1 day of surgery was defined as receiving at least 5 units of RBCs, which was the same as the previous definition of MBT within 24 hours after surgery, and was independently related to the postoperative adverse events.\(^{14,51}\) (1 unit RBC from 200mL whole blood)

2.3. Statistical analyses

All analyses were performed using SPSS 22.0. Categorical variables were expressed as frequencies (percentages), and performed using the Chi-square test with Yates correction or Fisher exact test, as appropriate. Normally distributed data were reported as mean ± standard deviation and compared between groups by Student t test. Skewed data were expressed as median (interquartile range) and compared between groups by Mann-Whitney U test. Variables associated with \(P<.05\) in univariate logistic regression were included in regression model. Multivariable logistic regression models were fitted using forward stepwise selection methods, and \(P<.05\) was considered statistically significant.

3. Results

3.1. Patients’ characteristics

A total of 324 adult patients with cardiac disease who underwent cardiac surgery were screened. Of these, 204 patients were excluded because they didn’t undergo CABG; their medical records were incomplete; or they did not do the rapid thrombelastography measurements before surgery. In the end, 120 patients were included in the analysis, of whom 24 (20.0%) underwent MBT during surgery, and 26 (21.7%) received MBT within 24 hours after surgery (Fig. 1).

Demographic variables of the patients were given in detailed in Table 1. The average age of patients was 61.6 ± 7.6 years (range of 48–82), including 92 male and 28 female. Hypertension (71.7%) was the most common comorbidity. All chronic medications were recorded and had no effect on MBT no matter undergoing during or after surgery (Tables 2 and 4). No patient in our study received preoperative RBC transfusion. During surgery, 58 (48.3%) patients did not receive any transfusion, while the remaining 62 (51.7%) received a total of 215 RBC units, with each patient receiving an average of 3.5 units. Within 1 day after surgery, 56 (46.7%) patients did not receive any transfusion, while the remaining 64 (53.3%) received a total of 316 RBC units, with each patient receiving an average of 4.9 units.

3.2. Influencing factors of MBT during CABG

According to the univariate analysis (Table 2), the factors associated with MBT during surgery were female \((P=.001)\), smoking \((P=.023)\), diabetes \((P=.031)\), lower preoperative Hb level \((P=.001)\), longer CPB time \((P=.003)\), and higher maximum clot strength (MA) level \((P=.001)\). Multivariate logistic regression analysis (Table 3) demonstrated that lower preoperative Hb level \((P<.001)\) and longer CPB time \((P<.001)\) were the independent risk factors for MBT during surgery. No components of the r-TEG predicted MBT during surgery.

MBT incidence increased with decreasing preoperative Hb level (Fig. 2A). Incidence was 10.7% among patients with Hb \(\geq 110\) g/L; but it increased sharply from 23.1% at Hb \(\geq 110\) g/L, to 50.0% at Hb \(<110\) g/L. Longer CPB was associated with increased MBT risk (Fig. 2B). Each 20-minute prolongation of CPB increased MBT incidence by 0.5 to 1 time. When CPB duration exceeded 100 minutes, the incidence of MBT increased sharply from 12.5% to 25.0%. When it exceeded 120 minutes, the incidence of MBT increased most, from 25.0% to 38.5%.

3.3. Influencing factors of MBT within 24 hours of CABG

Univariate analysis (Table 4) showed that the factors associated with MBT within 24 hours of surgery were older age \((P=.016)\), female \((P=.039)\), lower preoperative Hb level \((P<.001)\), lower preoperative hematocrit level \((P=.002)\), longer thrombin time \((P=.047)\), less ABT \((P<.001)\), longer ACT \((P<.001)\), and longer k-time (speed of clot formation) \((P=.007)\). Multivariable logistic regression analysis (Table 5) indicated that longer ACT \((P<.001)\), less ABT \((P<.001)\), and older age \((P=.008)\) were the independent risk factors for MBT within 24 hours of surgery.

MBT incidence generally increased with increasing ACT (Fig. 3C). No MBT event occurred among patients with ACT <90 seconds, but it increased sharply from 12.9% at ACT <110
Table 2

Univariate analysis of massive blood transfusion (MBT) during CABG.

| Feature                                      | MBT (n = 24) | No MBT (n = 96) | P-value |
|----------------------------------------------|--------------|----------------|---------|
| **Demographics:**                           |              |                |         |
| Age (yr)                                     | 61.0 ± 5.0   | 61.7 ± 8.1     | .589    |
| Female, n (%)                                | 12 (50.0)    | 16 (16.7)      | .001    |
| Body mass index (kg/m²)                      | 22.7 ± 3.5   | 23.7 ± 2.7     | .124    |
| Smoking                                      | 4 (16.7)     | 40 (41.7)      | .023    |
| Alcohol consumption                          | 4 (16.7)     | 22 (22.9)      | .506    |
| **Clinical Characteristics:**                |              |                |         |
| Comorbidities, n (%)                         |              |                |         |
| Hypertension                                 | 16 (66.7)    | 70 (72.9)      | .543    |
| Diabetes                                     | 12 (50.0)    | 26 (27.1)      | .031    |
| Myocardial infarction                        | 2 (8.3)      | 14 (14.6)      | .523    |
| Cerebral infarction                          | 2 (8.3)      | 12 (12.5)      | .733    |
| Hepatic insufficiency                        | 1 (4.2)      | 8 (8.3)        | .685    |
| Renal dysfunction                            | 10 (41.7)    | 24 (25.0)      | .105    |
| Hyperlipemia                                 | 12 (50.0)    | 36 (37.5)      | .264    |
| Coronary stenting                            | 2 (8.3)      | 10 (10.4)      | >.99    |
| Diameter of left atrium (mm)                 | 35.6 ± 6.2   | 35.6 ± 5.4     | .974    |
| Left ventricular ejection fraction (%)       | 53.7 ± 12.7  | 56.3 ± 12.6    | .352    |
| NYHA class III-IV, n (%)                     | 20 (83.3)    | 64 (66.7)      | .111    |
| ASA II-V, n (%)                              | 22 (91.7)    | 78 (81.3)      | .358    |
| **Medications, n (%)                         |              |                |         |
| ACEI/ARB                                     | 12 (50.0)    | 32 (33.3)      | .130    |
| β-adrenergic receptor blockers               | 18 (75.0)    | 74 (77.1)      | .829    |
| Calcium channel blockers                     | 8 (33.3)     | 42 (43.8)      | .355    |
| Nitrates                                     | 18 (75.0)    | 68 (70.8)      | .685    |
| Antiplatelet drugs                           | 4 (16.7)     | 26 (27.1)      | .292    |
| Anti-coagulants                              | 22 (91.7)    | 82 (85.4)      | .523    |
| Digoxin                                      | 4 (16.7)     | 8 (8.3)        | .255    |
| Diuretics                                    | 10 (41.7)    | 30 (31.3)      | .333    |
| Lipid-regulating drugs                       | 22 (91.7)    | 76 (79.2)      | .239    |
| **Laboratory data:**                         |              |                |         |
| Haemoglobin (g/L)                            | 119.1 ± 17.5 | 131.0 ± 15.3   | .001    |
| Platelets count ( × 10³/μL)                  | 182.2 ± 56.5 | 181.4 ± 42.9   | .938    |
| Hematocrit (%)                               | 37.1 ± 4.5   | 38.8 ± 5.0     | .129    |
| Prothrombin time (s)                         | 11.4 (10.4, 11.9) | 10.9 (10.6, 11.5) | .520 |
| Abnormal INR, n (%)                          | 4 (16.7)     | 12 (12.5)      | .737    |
| Activated partial thrombokinase time (s)     | 32.8 (30.2, 37.7) | 33.0 (30.0, 34.3) | .306 |
| Thrombin time (s)                            | 13.7 (13.1, 14.9) | 13.6 (12.7, 14.2) | .176 |
| Fibrinogen (mg/mL)                           | 387.7 ± 102.2 | 342.7 ± 71.7   | .072    |
| **Surgical factors:**                        |              |                |         |
| Emergency status, n (%)                      | 4 (16.7)     | 10 (10.4)      | .476    |
| Duration of operation (min)                  | 485.4 ± 57.2 | 482.5 ± 54.7   | .645    |
| Cardiopulmonary bypass (min)                 | 115 ± 21.3   | 96.6 ± 27.3    | .003    |
| Concomitant procedure, n (%)                 | 4 (16.7)     | 16 (16.7)      | >.99    |
| Autologous blood transfusion (mL)            | 470 (187.5, 637.5) | 500 (250, 500) | .851    |
| **Preoperative r-TEG**                       |              |                |         |
| ACT (s)                                      | 105.0 (105.0, 122.8) | 105.0 (97.0, 121.0) | .155 |
| K-time (min)                                 | 0.8 (0.8, 1.1) | 0.8 (0.8, 1.1) | .700    |
| Angle (deg)                                  | 78.7 (78.1, 81.2) | 78.7 (76.1, 79.8) | .185 |
| MA (mm)                                      | 75.9 (73.2, 77.6) | 72.1 (70.0, 74.0) | .001    |

Where applicable, results are expressed as median (range). Other values in parentheses are percentages.

**ACEI** = angiotensin converting enzyme inhibitor, **ACT** = activated clotting time, **ARB** = angiotensin II receptor blockers, **ASA** = American Society of Anesthesiologists grade, **INR** = international normalized ratio, **MA** = maximum clot strength, **NYHA** = New York Heart Association.

Table 3

Multivariate analysis of massive blood transfusion (MBT) during CABG.

| Factors                                      | Regression coefficient (B) | P-value | OR   | 95% CI          |
|----------------------------------------------|-----------------------------|---------|------|---------------|
| CPB duration, per 10 min                     | 0.387                       | .001    | 1.473| 1.178–1.841   |
| Hemoglobin, per 10 g/L                       | −0.680                      | .001    | 0.507| 0.345–0.745   |

CI = confidence interval, CPB = cardiopulmonary bypass, OR = odds ratio.
seconds, to 33.3% at ACT ≥110g/L. Among patients with ACT ≥150 seconds, 60% received MBT. More ABT was associated with lower MBT risk (Fig. 3D). When ABT <200 mL, the incidence of MBT was as high as 50%. MBT decreased sharply from 36.4% to 8.1% when ABT exceeded 400 mL. Moreover, increasing age was associated with increased MBT incidence (Fig. 3E). Incidence was 14.3% among patients under the age of 60, but it increased sharply from 21.2% among patients aged 60 to 69 to 50.0% among those at least 70 years old.

4. Discussion

Based on the average transfusion of 3.5 and 4.9 units respectively in patients who received transfusion during surgery and within 1 day after surgery, intraoperative MBT was defined as at least 4 units of RBCs transfusion, and postoperative MBT was defined as at least 5 units, which was consistent with the thresholds in previous reports,[6,14] and the results were worthy for reference. In our study, 20% of patients received MBT and accounted for 55.8% of the total units of allogeneic RBCs consumed during surgery, meanwhile 21.7% of patients received MBT and accounted for 67.1% of the total units of allogeneic RBCs consumed within 1 day of surgery. These findings also provided strong support for the view that reducing MBT can significantly reduce the overall demand for blood products.[6] In order to evaluate the utility of r-TEG to predict MBT in patients undergoing CABG more definitely, we analyzed the risk factors of MBT in different time periods.

Results showed that all components of the r-TEG failed to predict MBT during surgery. Although preoperative MA was an independent predictor in the linear regression model, it did not remain so in the final logistic regression model. Perhaps, because increased MA indicated a hypercoagulable state, which was related to the severity of coronary atherosclerotic heart disease (CAD) and may increase the difficulty and duration of surgery, but the effect on MBT was indirect, so it did not independently contribute to the model of massive transfusion more than did CPB time alone. Similar to the previous study,[13] we considered that preoperative r-TEG did not appear to be useful in predicting the MBT during CABG.

Lower preoperative Hb level and longer CPB were associated with an increased incidence of MBT during surgery, which have been reported previously.[6,14] In our research, MBT risk increased 1-fold for each 10 g/L decrease in Hb level. When the level of Hb was lower than that of 110 g/L, the MBT incidence increased sharply from 23.1% to 50.0%. Huang et al[6] also believed that a large jump in MBT incidence occurred when Hb level decreased to <110 g/L. Therefore, reducing RBC consumption substantially will require increasing preoperative Hb levels, preferably above 110 g/L.[15] Besides, MBT risk increased by 47% for each 10-minute prolongation of CPB, even higher than the 15% increase reported previously.[6] We observed sharp increases in MBT incidence for CPB lasting longer than 110 or 120 minutes. In contrast, only 6.7% of patients with CPB shorter than 80 minutes required MBT. Our findings suggest that CPB should be as short as possible, preferably within 100 minutes.

In our study, r-TEG ACT was associated with an increased incidence of MBT within 1 day after surgery. We found a 1.5-fold increase in MBT risk for each 10-minute prolongation of ACT, and it increased sharply from 12.9% to 33.3% when ACT reached over 110 s. The ACT was increased with factor deficiency or severe hemodilution.[10] On the basis of previous histological assessment of atherosclerotic lesions with microthrombosis,[16,18] greater consumption of coagulation factors was likely to lead to a decrease in concentrations seen in patients with more severe CAD.[20] Additionally, coagulation factors were further reduced owing to hemodilution and consumption after cardiac surgery with CPB.[12] We had reason to believe that low concentration of coagulation factors was the possible cause of postoperative MBT. Waldemar et al[23] confirmed that preoperative extrinsically activated test, especially clotting time, was useful in predicting an increased likelihood of postoperative bleeding in patients undergoing CABG. Likewise, we suggested that r-TEG can predict the MBT in the early postoperative period of CABG. And supplementation of plasma or coagulation factors was necessary to reduce ACT, preferably within 110 seconds. In addition, we assessed interaction by logistic regression model, and use NYHA class to represent the severity of CAD. The results showed that there was no interaction between ACT and severity of CAD (ACT by NYHA class, P=.562), and no interaction between ACT and CPB time (ACT by CPB time, P=.281).

Previous studies[24,25] have determined that ABT can reduce blood loss and allogeneic blood transfusion. Its application in surgeries could moderately improve early postoperative Hb levels and tissue oxygenation.[26,27] We found that ABT decreased risk of postoperative MBT by approximately 30% with each 100 mL increase. In agreement with earlier reports,[28] intraoperative blood salvage was an effective method to reduce the postoperative MBT. Older age has also been demonstrated to be associated
with more postoperative blood transfusion, which may be related to a greater likelihood of complications. In our sample, the incidence of MBT was as high as 50% among patients at least 70 years old, which was about 3-fold higher than that among younger patients. Accordingly, it was of high importance to optimize perioperative care, particularly in the elderly.

As shown in our results, the failure to predict the perioperative MBT during surgery using r-TEG components could be
attributed to the following factors. According to our data, the median ACT was 128 seconds in patients with postoperative MBT, and was 105 seconds in patients without postoperative MBT. We found that 8 patients with ACT >128 seconds did not receive postoperative MBT. These patients had a mean age of 60.8 years, and all of them received ABT more than 500 mL. The lower age levels and larger ABT may be the reasons why patients with longer ACT did not need MBT. Besides, 4 patients with ACT <105 seconds received postoperative MBT, with an average age of 76.5 years and an average ABT volume of 250 mL. The older age and less ABT may be the reasons why patients with shorter ACT need MBT. Therefore, we should integrate multiple factors comprehensively to evaluate the requirements for MBT. Besides, preoperative K-time and angle which mainly reflected the fibrinogen level showed no significant correlation with postoperative MBT. The level of fibrinogen was also reduced during CPB secondary to dilution, but the transformation of fibrinogen to brin was typically not impaired, suggesting that fibrinogen was not usually a significant problem.[30] Previous studies have indicated that patients with coronary heart disease were in a state of hypercoagulability, with high platelet count and platelet function.[31] In our research, the median of preoperative MA in patients with postoperative MBT (74.0 mm) was even higher than that without postoperative MBT (72.1 mm). Thus, the higher MA may be associated with the increased blood clotting, but would not cause postoperative MBT. In addition, all components of the r-TEG failed to predict MBT during surgery. The possible reason may be that surgery-related factors (such as CPB, surgical damage, etc.) were the most direct cause of intraoperative MBT, while r-TEG’s prediction of intraoperative MBT was indirect, so the correlation between components of the r-TEG and intraoperative MBT was not significant.

There are several study limitations, one of them being that it was retrospective in nature, which may have led to biased selection of patients. Besides, the number of participants was quite low, and further studies were needed to investigate our observation in a larger group of patients. As well as the study population was also heterogeneous, for instance, gender ratio was mismatched. However, these results were from a consecutive series of cases and so male dominance was unpredictable. In addition, this study only applied to pre-operative r-TEG and not intraoperative r-TEG or postoperative r-TEG. The effect of intraoperative and postoperative r-TEG should be explored and discussed in further studies. Moreover, the findings of r-TEG cannot be applied to ROTEM. Finally, if the thromboelastometry tests could be performed before and during CABG, there will be additional costs to cover reagents and maintenance, and this economic factor might be difficult to accept in some centers.

5. Conclusions

Based on the analysis of the presented results, preoperative r-TEG ACT can predict the increase of postoperative MBT in patients undergoing CABG. We recommend the careful monitoring of coagulation system with r-TEG, which allows rapid diagnosis of coagulation abnormalities even before the start of surgery.

Author contributions
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