Original Article

Hemoadsorption of Rivaroxaban and Ticagrelor during Acute Type A Aortic Dissection Operations

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Objective: To analyze the results of hemoadsorption in patients with cardiac surgery to thoracic aortic surgery, who had been loaded beforehand with either Factor Xa inhibitor *rivaroxaban* or P2Y12 receptor antagonist *ticagrelor*.

Methods: We investigated 21 of 171 consecutive patients (median age 71 [interquartile range 62, 76] years) who underwent emergency cardiac operations for acute type A aortic dissection between 2014 and 2020. These patients were pretreated with rivaroxaban (n = 9) or ticagrelor (n = 12). In ten of 21 cases (since 2017), we installed a hemoadsorber into the heart–lung machine and compared the results to eleven patients done without hemoadsorber before that time.

Results: The operation time was significantly shorter in the adsorber group (286 ± 40 min vs. 348 ± 79 min; p = 0.045). The postoperative 24-hour drainage volume was significantly lower after adsorption (p <0.001; 482 ± 122 ml vs. 907 ± 427 ml) and no rethoracotomy had to be performed (compared to two rethoracotomies [18.9%] among patients without adsorber use). Also, patients without hemoadsorption required significantly more platelet transfusions (p = 0.049).

Conclusions: In patients with acute type A aortic dissection who were pretreated with rivaroxaban and ticagrelor, the intraoperative use of CytoSorb hemoadsorption during cardiopulmonary bypass is reported for the first time. The method was found to be effective to prevent from bleeding and to improve the outcome in aortic dissection.

Keywords: aortic dissection, aortic surgery, bleeding complications, cardiac surgery, type A aortic dissection

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Introduction

Acute type A aortic dissection is a life-threatening condition with a mortality of 1%–2% per hour, increasing to 30%–68% within 48 hours. Emergency surgical treatment is the gold standard. However, a high rate of complications caused by malperfusion is reported[1–3)] and sometimes survival is compromised by pretreatment with coagulation-active substances. Generally, cardiac patients under anticoagulation therapy are at a higher risk of perioperative complications and serious bleeding. Major bleeding, an increased rethoracotomy rate, and the need for transfusion of blood products significantly impair the outcome after cardiac surgery. In particular,

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Table 1   Patients baseline data

	Non-adsorber group (n = 11)	Adsorber group (n = 10)	Total (n = 21)
Demography			
Female, n (%)	5 (45)	6 (60)	11 (52)
Age (years), median (IQR)	62 [61, 73]	75 [71, 78]	71 [62, 76]
Body mass index (kg/m²), median (IQR)	26.0 [25.5, 28.5]	25.0 [23.0, 27.0]	26.0 [23.0, 27.0]
Comorbidities, n (%)			
Hypertension	9 (81.8)	10 (100)	19 (90.5)
Dyslipidaemia	4 (36.4)	2 (20.0)	6 (28.6)
IDDM	1 (9.1)	0 (0)	1 (4.8)
COPD	1 (9.1)	3 (30.0)	4 (19.0)
Nicotine	1 (9.1)	5 (50.0)	6 (28.6)
PAD	1 (9.1)	4 (40.0)	5 (23.8)
Creatinine clearance (mg/dl), n (%)			
>85	2 (18.2)	0 (0)	2 (9.5)
50–85 ml/h	6 (54.5)	9 (90.0)	15 (71.4)
<50 ml/h	3 (27.3)	1 (10.0)	4 (19.0)
LVEF, n (%)			
>50%	10 (90.9)	9 (90.0)	19 (90.5)
31–50%	1 (9.1)	1 (10.0)	2 (9.5)
21–30%	0 (0)	0 (0)	0 (0)
Log EuroSCORE II	10.6 [7.4, 17.8]	17.1 [7.6, 19.1]	12.4 [7.1, 19.1]
GERAADA score	13.9 [11.1, 20.6]	14.9 [13.0, 20.1]	14.3 [11.1, 20.4]

Comparison of patients among groups: Adsorber group = Cytosorb adsorption and non-adsorber group = without Cytosorb adsorption. IQR: interquartile range; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: left ventricular ejection fraction; IDDM: insulin-dependent diabetes; COPD: chronic obstructive pulmonary disease; PAD: peripheral arterial disease; GERAADA: German Registry for Acute Aortic Dissection Type A

large quantities of blood products and prolonged operation times must be regarded as key issues. Both are essential triggers for prolonged postoperative progress.[4–6]

It is generally agreed that bleeding complications during cardiac surgery must be reduced to an absolute minimum. However, if, for example, a patient with atrial fibrillation or shortly after percutaneous coronary intervention (PCI) acquires an acute type A aortic dissection, cardiac surgeons will have to operate in the presence of direct acting (novel) oral anticoagulants or p2Y12 inhibitors. The efficiency and safety of these drugs has been shown in several randomized trials.[7–10] Especially since the PLATO[7] and ROCKET-AF[10] trials were published, surgeons are often confronted with ticagrelor- or rivaroxaban-loaded patients. Strategies to reduce bleeding complications in anticoagulative pretreated patients are therefore needed, especially in the field of emergency cardiac operations such as type A aortic dissection. We therefore analyzed the outcomes of using the CytoSorb adsorber (CytoSorbents Corporation, Monmouth Junction, NJ, USA) installed into a side circuit of the heart–lung machine (HLM) to remove ticagrelor and rivaroxaban from the patient's blood by hemoadsorption during the cardiopulmonary bypass (CPB). Its ability to adsorb coagulation active substances has been

demonstrated previously.[11] We investigated and here describe in detail the effects of adsorption in the emergency setting to decrease bleeding complications and to enhance the postoperative outcome.

Patients and Methods

Patient population

The protocol for this retrospective study was approved by the Hamburg General Medical Council Ethics Committee: A retrospective analysis of 21 consecutive patients (median age 71 [interquartile range 62, 76] years) who underwent emergency cardiac surgery due to acute type A aortic dissection at our institution, between January 2014 and January 2020. Patients were either pretreated with ticagrelor (n = 12) or rivaroxaban (n = 9). They represented 12.3% of 171 patients with acute type A aortic dissection whom we operated on during this period (n = 150 had neither ticagrelor nor rivaroxaban). Since June 2017 (in 10 of 21 cases), we installed a standardized CytoSorb adsorber into CPB and compared the clinical results with those of 11 patients treated without the CytoSorb adsorber before that time. CytoSorb consists of biocompatible porous polymer beads able to remove substances from blood,

based on pore capture and surface adsorption. It has the CE Mark approved under the Medical Devices Directive (ISO 10993 biocompatible, manufactured in the United States under ISO 13485 certification).

The baseline characteristics of these 21 patients are listed in **Table 1**. The adsorber group included 6 patients who had been treated with ticagrelor because of a suspicion of an acute coronary syndrome. In 3 of these 6 patients, a diagnostic coronary angiography had been conducted. Malperfusion of the coronary vessels occurred in 2 of 3 patients. The non-adsorber group also included 6 patients who were pretreated with ticagrelor, four of them also because of a suspected acute coronary syndrome. The vast majority (n = 8) of the rivaroxaban pretreated patients were preoperatively anticoagulated because of atrial fibrillation. In one case, the indication for anticoagulation was given because of a pulmonary embolism.

Patient management

Diagnosis was confirmed by computer tomography in all cases. Thereafter, all patients were treated as high emergency cases and were brought immediately to the operating theater. Transesophageal echocardiography was done intraoperatively under general anesthesia. The median sternotomy was followed by pericardiotomy. During preparation of CPB, the adsorber was installed in the HLM system under sterile conditions (**Fig. 1**). The CPB was performed with retrograde femoral arterial cannulation or directly in the aorta after echocardiography and sliding technique under echocardiography control. The flow through the adsorber was "active" when the patient's blood was taken from the venous return to the HLM. The blood was then pumped through the adsorber into the venous return flow of the patient using a roller pump at 500 ml/min. After aortic clamping and induction of cardiac arrest, antegrade myocardial protection was performed with either Bretschneider or cold blood cardioplegia. After deep hypothermia (<22 °C), circulatory arrest with retrograde or antegrade head perfusion was performed. Surgical management of the distal aortic repair depended on the extent of the intimal tear. We documented all preoperative clinical data to be evaluated in the context of the adsorber, and the following data were collected and documented: type, dates, and outcomes of open-heart surgery. The rates, severity, and management of periprocedural bleeding complications were documented in detail. In addition, the number of blood products, drainage volumes during the first postoperative 24 hours, and reoperations for bleeding were documented.

Fig. 1 The demonstration of including the CytoSorb adsorber into the CPB circuit of the HLM. The adsorber is made of biocompatible porous polymer beads able to remove substances from whole blood based on pore capture and surface adsorption by using a roller pump and optimal blood flow rate at 500 ml/min. CPB: cardiopulmonary bypass; HLM: heart–lung machine

Rethoracotomy was performed if >1.000 ml drainage volume occurred over 6 hours without a tendency for improvement and a suspicion of arterial bleeding. Furthermore, we noted days in the intensive care unit (ICU), total length of stay, and 30-day mortalities (cardiac/non-cardiac death). Ongoing resuscitation and severe sepsis were general exclusion criteria for the study. All relevant baseline clinical data are given in **Table 1**.

Statistical data analysis

Statistics and calculations were performed with the statistical analysis software R (R Core Team 2020. R: A Language and Environment for Statistical Computing. Vienna, Austria). Metric data were summarized with medians, and 25th and 75th percentiles. Categorical and ordered data are shown with frequencies and proportions. The statistics are summarized by the application of adsorber (yes/no) and medications (rivaroxaban or ticagrelor). Differences between drainage volumes are shown with boxplots. Drainage volume, procedure time, rethoracotomy, transfusion of platelets, as well as days in the ICU and the hospital were compared between patients with and without adsorber and across medications. The differences between logarithmically transformed drainage volumes and procedure time were examined with linear regression models. Rethoracotomies were compared using the Fisher's exact test. A generalized linear (quasi-) Poisson regression was applied to examine

transfusion units of platelets, and days in the ICU and hospital across groups. All p-values were two sided, and a p-value <0.05 was considered significant.

Results

The surgical procedure included replacement of the ascending aorta in all cases, additional hemiarch replacement in 5 (23.8%) of 21 cases, and total arch replacement in 5 (23.8%) cases. In 3 of 21 patients (14.3%), a combined procedure with coronary artery bypass grafting (CABG) was carried out. In the non-adsorber group (n = 11), all patients were treated with a replacement of the ascending aorta. In 3 (27.3%) patients, we had to replace the complete aortic arch, and 3 (27.3%) patients needed an aortic hemiarch replacement. Three (27.3%) patients got an additional CABG. In the adsorber group (n = 10), also all patients were treated with a replacement of the ascending aorta. In 2 (20.0%) patients, we had to replace the aortic arch. Two (20.0%) patients needed a hemiarch replacement. An additional CABG procedure was not necessary in this group. All relevant details of surgery are given in **Table 2**. The mean cross-clamp time was 141 ± 80 min in adsorber patients and 143 ± 45 min in the others; the mean CPB time without adsorption was 203 ± 65 min and that with adsorption for 207 ± 45 min. Nevertheless, in the non-adsorption group, the total operation time was significantly longer: 348 ± 79 min vs. 286 ± 40 min (p = 0.045). The difference in total operation time between medication in the respective group was non-significant (shorter in adsorber patients: with ticagrelor, 272 ± 35 min and with rivaroxaban, 307 ± 43 min). Further, the 24-hour drainage volume was significantly lower in adsorber patients (p <0.001; 750 [635, 965] ml vs. 475 [428, 508] ml; **Fig. 2**). Comparing adsorber and drug treatment groups, there was a significant difference in drainage volume between patients with rivaroxaban exposure (p = 0.044) and those without. No rethoracotomy because of bleeding needed to be performed (compared to two rethoracotomies [18.9%] among patients without adsorption, p = 0.476). One of them was treated with ticagrelor and another one was under a rivaroxaban regime. Eight of 11 patients without adsorption needed transfusion of red blood cells, whereas only 6 of 10 patients with adsorption needed transfusion (p = 0.429). In addition, patients without adsorption needed significantly more platelet transfusions (p = 0.049).

Thirty-day mortality was 19.0% (4 of 21 patients), where 2 of them had been treated with rivaroxaban (22.2%). In the adsorber group, there was only 1 death at day 5 (10.0%). The patient had been treated with rivaroxaban. Among patients operated without adsorption, there were 3 deaths (27.3%). One was a 77-year-old woman with readmission after discharge for new infectious double endocarditis. Reoperation with replacement of the ascending aortic prosthesis and valve surgery were performed. She died of organ failure on day 6. The second case was a 67-year-old woman who died on day 3. The patient had a rethoracotomy due to an increased drainage volume within the first 6 hours of surgery. She had been pretreated with ticagrelor. An increased transfusion was necessary (transfusion of 6 units of red blood cells and 5 platelet units). The patient died postoperatively under the conditions of excessive catecholamines and low perfusion. The third case involved a 79-year-old woman with postoperative systemic inflammatory response syndrome (SIRS) and low cardiac output at day 17.

Patients with symptomatic malperfusion syndrome showed results as follows: This selection included 9 of 21 patients (42.9%). The mortality in this group was 3 out of 9 (33.3%). The risk calculation using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) was 24.9% ± 15.9%, and the German Registry for Acute Aortic Dissection Type A (GERAADA) score was 46.8% ± 31.15%.

Four out of 9 patients with malperfusion belonged to the adsorber group. Interestingly, the stay in the ICU for patients belonging to the adsorber group with symptomatic malperfusion was shorter than in that for non-adsorber patients (5.5 ± 7.8 vs. 8.6 ± 11.1 days).

Neurological dysfunction was observed postoperatively in 5 patients (3 of 5 patients with temporary dysfunction and 2 patients with permanent dysfunction). One patient in the non-adsorber-group had a wound infection in the groin above the femoral artery, and in the adsorber group, 1 patient had a sternal wound infection. One patient had an unstable sternum and required reoperation. In the early stage after surgery, 1 patient developed pneumonia with prolonged ventilation >48 h. Stays in the ICU were generally shorter for the adsorber group (10.2 ± 7.6 vs. 8.0 ± 6.9 days; p = 0.528).

Discussion

The use of hemoadsorption in patients with acute type A aortic dissection under ticagrelor or rivaroxaban therapies is reported for the first time. Acute aortic dissection is a life-threatening situation that occurs with sudden onset due to an intimal tear between layers of the aortic

Table 2   Details of surgery and early postoperative data

|	Non-adsorber group (n = 11)	Adsorber group (n = 10)	Total (n = 21)
Surgery procedure, n (%)			
Ascending replacement	11 (100)	10 (100)	21 (100)
Hemiarch replacement	3 (27.3)	2 (20.0)	5 (23.8)
Total arch replacement	3 (27.3)	2 (20.0)	5 (23.8)
Coronary bypass	3 (27.3)	0 (0)	3 (14.3)
Time-related outcomes, mean ± SD			
BPT, min	203 ± 65	207 ± 45	205 ± 55
ACC, min	141 ± 80	143 ± 45	142 ± 64
Procedure time, min	348 ± 79	286 ± 40	318 ± 70
Transfusion of platelet, n (%)			
0	1 (9.1)	4 (40.0)	5 (23.8)
>1	10 (90.9)	6 (60.0)	16 (76.2)
Transfusion of red blood cells, n (%)			
0	3 (27.3)	4 (40.0)	7 (33.3)
>1	8 (72.8)	6 (60.0)	14 (66.7)
Outcome data, median (IQR)			
Drainage volume/24 h (ml)	750 [635, 965]	475 [428, 508]	620 [460, 750]
Days in intensive care	9 [6, 10.5]	4 [4.0, 9.0]	6 [4, 10]
Total length of stay, days	15 [14, 16]	16 [12, 23]	15 [12, 23]
Rethoracotomy rate, n (%)	2 (18.2)	0 (0)	2 (9.5)
30-day death, n (%)	3 (27.3)	1 (10.0)	4 (19.0)

BPT: bypass time; ACC: aortic clamping time; SD: standard deviation; IQR: interquartile range

wall. This condition is very challenging to treat. Goals of acute type A aortic dissection surgery are 1) to excise the intimal tear, 2) decrease the obliterate blood flow into the false lumen, 3) replace the ascending aorta and/or aortic arch, 4) restore aortic valve competence, and 5) to correct malperfusion. Generally, aortic surgery, where increased bleeding risk is the result of emergency surgery; multiple suture lines; prolonged CPB; hypothermia; and existing metabolic acidosis[12] are often accompanied by transfusion of blood products. Usually, patients with anticoagulative pretreatment have a higher risk of preoperative complications and a high risk of serious bleeding and major bleeding complications. This can impair the outcome after cardiac surgery. Coagulopathy therapy is still the most challenging in emergency situations. The transfusion of blood products is associated with increased mortality, extended ventilator support, and transfusion-related serious lung or renal failure; furthermore, it has an influence on infections, cardiac complications, and neurological events.[13,14]

Platelet transfusions in patients under pretreatment with ticagrelor in emergency surgery cannot be a definitive solution because ticagrelor and active metabolites are still present at the time of the transfusion.[15,16] Moreover, they are able to inhibit new platelets because of reversible binding of the drug. However, a reduction in

bleeding complications should be carried out as a priority collaboration between the cardiothoracic surgeon, the anesthesiologist, and the perfusionist.[17]

In vitro data on the use of sorbent hemoadsorption as an alternative option for removal of ticagrelor from the blood are available.[18] Our recent investigation has shown the benefit of adsorption in patients with coagulation-active substances.[11] However, there are still
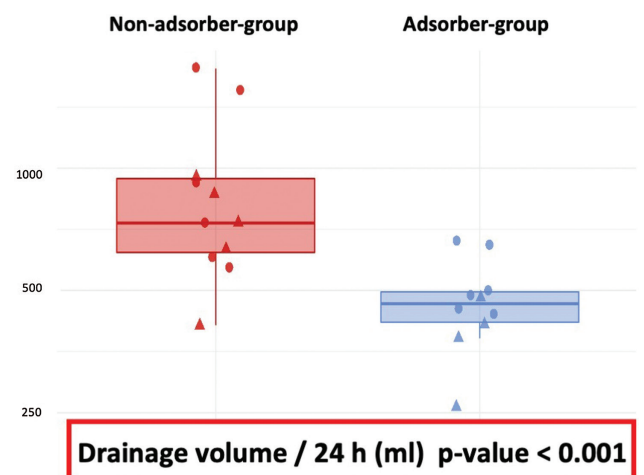
Fig. 2   The 24-hours drainage volume was significantly lower in adsorber patients; patients treated with ticagrelor ○ or rivaroxaban △ and with hemadsorption (blue) and without hemadsorption (red).

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open questions, e.g., how much adsorption time is needed to remove the drugs. In addition, the adsorption of other drugs needs to be investigated. However, the hemoadsorption technique – highly effective in removing ticagrelor – is a potent option for reducing bleeding complications. Recent research data evaluated the negative effects of ticagrelor in patients with misdiagnosed acute aortic dissection.[19] Treatment with double antiplatelet therapy in these cases was common. Even if patients pretreated with ticagrelor were not associated with higher mortality, there was a significantly higher bleeding tendency during surgery and a trend toward higher rates of surgical revision.[19]

In addition to the EuroSCORE, we included the TEM classification[20] and GERAADA score[21] in our analysis. The TEM classification characterizes the type of dissection (T), the localization of entries (E), and the failure of malperfusion (M) with clinically relevant symptoms. The GERAADA score is a web-based application for standard use. It is a tool to predict the 30-day mortality for patients undergoing surgery for acute type A aortic dissection.[21] The described classifications did not consider whether coagulopathy was present. However, it could be crucial for patient's outcome. Aortic surgery is known to be accompanied by extreme transfusion of blood products. Four of 9 (44.4%) patients with symptomatic malperfusion syndrome were in the adsorber group; it is remarkable therefore that they showed a shorter ICU stay than those in the non-adsorber group. The data suggest that the use of intraoperative adsorption influences favorably the postoperative course. This observation supports the findings of a study with similar results in patients undergoing aortic surgery with hypothermic circulatory arrest while using adsorbers.[22] Other retrospective research recommended the use of hemoadsorption in patients undergoing aortic surgery. The use led to a shorter duration of mechanical ventilation, and shorter ICU and hospital stays.[23] Comparing the rate of rethoracotomies between the two groups, we had none in the adsorber group and two in the non-adsorber group (18.9%). There was a correlation between rethoracotomy and complications: a rethoracotomy involves a second surgical procedure and is associated with the risk of transfusion of blood products. The probability of wound healing disorders also arises, and the stay at the ICU could be prolonged. These complications influence the postoperative outcome and costs may rise. Because of these relationships, it seems to be really important to avoid the risk of a rethoracotomy. However, to

unequivocally demonstrate that the use of the CytoSorb adsorber can eradicate the risk of rethoracotomy in anticoagulative pretreated patients undergoing surgical treatment due to a type A aortic dissection, more research data on a larger cohort of patients are required. Nevertheless, even if a definite conclusion cannot be drawn because of small numbers, this study highlights the potential for adsorption and its benefits in reducing bleeding complications in patients taking anticoagulants and shows positive effects in cases with malperfusion syndrome.

Limitations

This analysis was not undertaken to evaluate the results of medical benefit in emergency cardiac surgery. Instead, we focused on clinical effects of hemoadsorption of rivaroxaban and ticagrelor in emergency operations for acute type A aortic dissection. However, we dealt with only 21 patients and our experience relates to a single center, thereby limiting the breadth of conclusions. The patients were non-homogeneous regarding cardiac and extracardiac comorbidities and their risk profiles. Investigations of larger cohorts and follow-up investigations by other centers will be required to confirm these early results with larger populations.

Conclusion

In patients with acute type A aortic dissection who were pretreated with rivaroxaban and ticagrelor, the intraoperative use of CytoSorb hemoadsorption during CPB is reported for the first time. The method was found to be safe and effective in preventing major bleeding complications.

Disclosure Statement

The authors report no conflicts of interest in this study.

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