The treatment of heparin resistance with Antithrombin III in cardiac surgery

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Purpose: To report three patients who developed heparin resistance during cardiac surgery which was successfully managed with 1 000 U Antithrombin III (AT III).

Clinical features: We observed heparin resistance prior to cardiopulmonary bypass (CPB) in one patient and during the CPB in two patients. In the first patient who was scheduled for mitral valve replacement, although heparin was administered sequentially up to 500 U·kg⁻¹ prior the CPB, the ACT value was 354 sec. After 1,000 U ATIII were administered the ACT was 395 sec and CPB was initiated. The ACT remained between 496 and 599 sec throughout CPB and a total of 260 mg protamine sulfate was given. In the other two patients following 300 U·kg⁻¹ heparin, the ACT was up to 400 sec and CPB was initiated. During CPB, ACT were decreased 360 sec and 295 sec in patients II and III respectively. Although heparin was added 1,500 U, ACT increased to $\geq$ 400 sec could not be achieved. In the second patient ATIII activity was found 10%. After the administration of 1,000 U ATIII, ATIII activity was found to be 67% 40 min later and ACT were increased up to 400 sec.

There was no thrombosis within the extracorporeal circuit, additional heparin was not required, less protamine was administered ($\leq$ 3 mg·kg⁻¹) and no excessive postoperative bleeding was observed in all patients.

Conclusion: We recommend that AT III supplementation should be considered to manage heparin resistance prior or during CPB in patients undergoing open heart surgery.

Objectif : Présenter le cas de trois patients qui ont développé une résistance à l'héparine, pendant une intervention cardiaque, traitée avec succès avec 1 000 U d'antithrombine III (AT III).

Éléments cliniques : Chez l'un des patients, la résistance à l'héparine s'est manifestée avant la circulation extracorporelle (CEC), mais pendant la CEC chez les deux autres patients. Dans le cas du premier patient pour qui le remplacement de la valvule mitrale avait été planifié, le temps de coagulation activée (TCA) a été de 354 s malgré l'administration séquentielle d'héparine, jusqu'à 500 U·kg⁻¹ avant la CEC. Après l'administration de 1 000 U d'AT III, le TCA était de 395 s et la CEC a été amorcée. Le TCA est demeuré entre 496 et 599 s tout au long de la CEC et 260 mg de sulfate de protamine ont été administrés en tout. Chez les deux autres patients, la CEC a été instaurée à la suite de l'administration de 300 U·kg⁻¹ d'héparine alors que le TCA allait jusqu'à 400 s. Pendant la CEC, le TCA est baissé à 360 s et 295 s chez les patients II et III, respectivement. En dépit de 1 500 U d'héparine supplémentaires, le TCA n'a pu être augmenté à 400 s. Chez le deuxième patient, l'activité de l'AT III était de 10 %. L'administration de 1 000 U d'AT III a amené l'activité de l'AT III à 67 %, 40 min plus tard, et les TCA se sont élevés jusqu'à 400 s. Chez tous les patients, il n'y a pas eu de thrombose à l'intérieur du circuit extracorporel, l'héparine supplémentaire n'a pas été nécessaire, l'administration de protamine a été faible ($\leq$ 3 mg·kg⁻¹) et il n'y a pas eu de saignements postopératoires excessifs.

Conclusion : Nous recommandons l'administration d'AT III supplémentaire pour traiter la résistance à l'héparine avant, ou pendant la CEC, lors d'interventions à coeur ouvert.

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COAGULATION is inhibited during cardiopulmonary bypass (CPB) to prevent thrombosis and its consequences. The anticoagulant of choice is heparin due to its prompt action and easy neutralization with protamine sulfate.^{1,2}

In some circumstances, large amounts of heparin (500 U·kg⁻¹) may be necessary to prolong the activated clotting time (ACT) to ≥ 400 sec. This is known as heparin resistance.^{3,4} Although infrequent, the cause of heparin resistance is incompletely defined.⁵⁻⁷

Heparin resistance was observed in three patients undergoing open heart surgery. In all cases anticoagulation was achieved during CPB with the administration of Antithrombin III (AT III, Atenativ) to treat heparin resistance.

Case 1

A 51 yr old woman was admitted for elective mitral valve replacement surgery. She had a history of rheumatic fever 25 yr earlier and dyspnea on exertion for five years. Premedication with 10 mg diazepam *po* was given one hour before surgery. Anesthesia was induced with etomidate, fentanyl and vecuronium and maintained with isoflurane, nitrous oxide in oxygen and supplemented with fentanyl. After sternotomy, 300 U·kg⁻¹ heparin sulfate (total 17,500 U) were administered into the right atrium before cannulation. The ACT value (Hemochron 801) was 83 sec just before heparin administration and 285 sec five minutes after heparin. Despite sequential heparin administration (150,000 U), ACT increase to ≥ 400 sec could

not be achieved. AT III 1,000 U was given and 15 min later the ACT value was 395 sec and CPB was initiated. Heparin sulfate 5,000 U was added to the priming solution. The ACT was > 400 sec throughout CPB and the case progressed uneventfully. The patient was successfully weaned from CPB and residual circulating heparin was neutralized with 200 mg protamine sulfate using the individual protamine dose-response curve via the peripheral route. The control ACT value was 95 sec (Table I). The aortic cross-clamp time was 42 min and the total CPB time was 55 min. At the end of the operation the trachea was extubated in the operating room and she was transferred to the intensive care unit (ICU). The total drainage from the chest tube after surgery was 650 ml/24 hr. The patient was discharged seven days after the operation.

Case 2

A 43 yr old man was admitted with unstable angina. He had a history of severe chest pain nine days before admission. Cardiac catheterization revealed severe triple-vessel coronary artery disease. Seven days after medical management with heparin sulfate (5,000 U, three times per day *sc*), he was scheduled for CABG. Heparin was stopped one day before surgery.

Premedication was with 10 mg diazepam *po*. Anesthesia was induced with 17 mg etomidate, 0.15 mg fentanyl and 5 mg vecuronium and maintained with nitrous oxide in oxygen, isoflurane and supplemental fentanyl. The ACT value was 103 sec. Heparin sulfate 300 U·kg⁻¹ was administered (total 29,000 U) into the right atrium. The ACT value was 395 sec after five min-

TABLE I Anticoagulation profile of the first patient

Time	ACT (sec)	Heparin given (U)	Total heparin (U·kg)	Temperature (°C)	Protamine given (mg)	Other
08:45	83			36.5		
09:00		17500	318			
09:10	285		409			
09:20		5000				
09:25	303		500			
09:35		5000				
09:40	346		590			
09:50		5000				
09:55	354					
10:05						AT III, 1000 U
10:20	395					CPB initiated
10:30	520			30		
10:45	599			31.5		
11:09	499					
11:15	496			37		CPB terminated
11:25					175	
11:35	111				25	
11:45	95					

utes and additional heparin sulfate, 5,000 U, was administered and CPB initiated. The pump prime had 5,000 U heparin sulfate added. After initiation of CPB, the ACT value was < 400 sec. Coagulation studies showed that prothrombin time (PT) was 27.5 sec, fibrinogen level was 173 mg·dl⁻¹ and AT III activity was 10% (normally 80-120%). Then, 1,000 U AT III was given and the ACT value increased to > 400 sec (445-485 sec) and, 20 min later, the AT III activity was 20% and 67% after 40 min (Table II).

Following coronary artery bypass grafting, the patient was weaned from CPB without difficulty. The aortic cross-clamp time was 68 min and CPB time was 110 min. After CPB, 260 mg protamine sulfate were administered, resulting in an ACT value of 103 sec. The trachea extubated in the operating room and the patient was transferred to the ICU. The total postoperative drainage was 750 ml and he was discharged ten days after surgery.

Case 3

A 58 yr. old woman was admitted suffering from a decrease in physical activity and tachycardia for two years. She was scheduled for aortic valve replacement and open mitral commissurotomy.

Induction and maintenance of anesthesia were as in the previous cases. After 25,000 U of heparin sulfate the ACT value was 314 sec. Additional 10,000 U heparin were administered, the ACT value 404 sec

and CPB was initiated. During CPB the ACT value decreased to 295 sec and despite the administration 15,000 U of heparin, ACT values ≥ 400 sec could not be achieved. After 1,000 U AT III were given to the patient ACT values increased to > 400 sec (407-547 sec) and CPB progressed uneventfully.

After aortic valve replacement and mitral commissurotomy, she was weaned from CPB without difficulty. The aortic cross-clamp time was 70 min, and the CPB time was 90 min. A total of 250 mg protamine sulfate was administered resulting in an ACT of 99 sec (Table III). She was transferred to the ICU, and the trachea was extubated after four hours. The total postoperative drainage was 550 ml. She was discharged on the seventh day postoperatively.

Discussion

Even though ACT may not reflect the circulating heparin level, it is commonly used to monitor the heparin effect on coagulation.^{7,8} The safe level of ACT for patients undergoing CPB has been empirically set by many groups at 400 sec.⁸⁻¹¹ Heparin resistance is defined as the failure of 500 U·kg⁻¹ to prolong the ACT to ≥ 400 sec. In the presence of heparin resistance, adequate anticoagulation by heparin may be unachievable. Inadequate heparinization during CPB can result in complications that range from subtle disturbances in the coagulation cascade to severe coagulopathy. Despite the presence of heparin, some

TABLE II Anticoagulation profile of the second patient

Time	ACT (sec)	Heparin given (U)	Total heparin (U·kg)	Temperature (°C)	Protamine given (mg)	Other
09:00	103			36.5		
09:25		29000	305			
09:30	398					
09:40		5000	357			
09:45	506					
09:55						CPB initiated
10:05	430			28		
10:20	380					
10:30		5000	401			
10:35	360					AT III, 1000 U
10:45		10000	515			
10:50	375					AT III activity: 10%
11:00						AT III 1000 U
11:05	385					
11:20	445			33		AT III activity: 20%
11:30	482			35		
11:45	485			36.5		AT III activity: 67%
11:50				37		CPB terminated
11:55	475					
12:05					260	
12:15	105					
12:30	103					

TABLE III Anticoagulation profile of the third patient

<i>Time</i>	<i>ACT (sec)</i>	<i>Heparin given (U)</i>	<i>Total heparin (U·kg)</i>	<i>Temperature (°C)</i>	<i>Protamine given (mg)</i>	<i>Other</i>
09:45	92			36.5		
10:00		25000	304			
10:05	314					
10:18		5000	365			
10:30	374					
10:45		5000	426			
10:55	404					
11:05						CPB initiated
11:10	295			33		
11:20		10000	548	26		
11:25	360					
11:35		5000	609			
11:40	390			26		
11:50	320					AT III 1000 U
12:00	407					
12:10	445					
12:20	506			35		
12:30	547					
12:35				37		CPB terminated
12:40	513					
12:45					250	
12:55	99					

coagulation activity and fibrin formation continues during CPB. The clinical consequences include excessive postoperative bleeding, intravascular coagulation and even thrombosis of the extracorporeal circuit.^{4,6}

We observed heparin resistance prior the CPB in one patient and during CPB in two others. Although heparin was administered sequentially up to 500 U·kg⁻¹, we could not prolong the ACT to ≥ 400 sec. The calculations used to determine the dose, the concentration of the heparin solution were confirmed to be correct.⁶

Many causes of increased heparin resistance, such as preoperative heparin and NTG therapy, infective endocarditis, intraaortic balloon counterpulsation, oral contraceptives, autotransfusion, ventricular aneurysm with thrombus have been reported.^{1,7,8,12,13} Three theories have been advanced to explain heparin resistance; heparin-induced thrombocytopenia, a heparin-induced decrease in the circulating AT III level and enhancement of factor VIII activity. Clinical heparin-induced thrombocytopenia usually occurs seven to ten days after the initiation of treatment and is thought to be the result of heparin-induced platelet antibodies. In this type of resistance over 50% have been associated with thromboembolism and 38% have been related to subsequent heparin resistance.¹²

We considered a decrease in AT III activity as the most likely of the heparin resistance. Measurement of AT III activity was only possible in the second patient and the decrease in AT III activity might have been due to heparin treatment for seven days before surgery. Other possible causes of the heparin resistance including primary or secondary AT III deficiency. Heparin alone has no effect on coagulation. It requires AT III to inhibit coagulation.^{5,6} AT III, a plasma α -2 globulin binds and inactivates thrombin, so that it is a potent inhibitor of blood clotting. A decrease in AT III concentration during CPB has been reported which may result in an abnormal response of heparin.^{14,15} Plasma AT III levels decrease by 17 to 33% when heparin is administered by intravenous or subcutaneous routes. The anticoagulant effect of heparin is insufficient when the plasma AT III level is $< 60\%$.¹⁶ Therefore, maintaining AT III in the normal range may be safer, not only for more complete coagulation activity suppression, but also for reducing the amount of heparin needed during CPB.¹⁴ Both Fresh Frozen Plasma (FFP) and banked plasma contain adequate levels of AT III, and infusion of blood products should correct antithrombin depletion and prolong the ACT suitably.^{1,12} Fresh frozen plasma has been used successfully to reverse heparin resistance in a patient with AT III deficiency.^{5,6}

Contrary to this report, no correlation was found between the plasma AT III activity and the prolongation in ACT after systemic heparinization with or without the addition of FFP.¹⁷ We preferred to administer AT III to treat the heparin resistance instead of FFP and achieved adequate anticoagulation after the AT III administration. Although it has been reported that AT supplementation that increased AT levels two-fold did not affect ACT values, supplemental AT III improved both quantitative and qualitative platelet parameters and produced increased ACT during CPB.^{14,18,19,20} In our patient AT III activity was increased from 10% to 67% and ACT increased to 400 sec. There was no thrombosis within the extracorporeal circuit and maintenance and weaning from the CPB were uneventful. In addition, less protamine was required ($\leq 3 \text{ mg}\cdot\text{kg}^{-1}$) to neutralize the heparin and no excessive postoperative bleeding was observed.

AT III is not recommended for routine use in cardiac surgery because of its extensive donor origin and potential transfusion risks. It is not indicated for patients who are at low risk for postoperative bleeding (short CPB time, single and primary procedures).

In conclusion, we recommend that AT III supplementation be considered to manage heparin resistance prior or during CPB in patients undergoing open heart surgery.

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