Addition of Acetylsalicylic Acid to Heparin for Anticoagulation Management During Pumpless Extracorporeal Lung Assist

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Pump-driven extracorporeal membrane oxygenation (ECMO) or pumpless arterio-venous interventional lung assist (iLA) is associated with possible complications, mainly consisting of bleeding or thrombosis/clotting by cellular deposits on the membrane or extracorporeal circuit surfaces, which may reduce gas-exchange capacity. In this study, we report our experiences with the addition of low-dose acetylsalicylic acid (ASA 1.5 mg/kg body weight/d) to heparin for anticoagulation of a pumpless low-resistance gas-exchange membrane (Novalung GmbH, Talheim, Germany). We assessed changes in coagulation parameters and the demand for transfusion of blood components. Furthermore, we compared the function of the artificial membranes (oxygen transfer and capacity of CO_2 removal) of the ASA group (n = 15) with that of a matched-pair control group treated with heparin alone. The mean duration of iLA treatment was 6.6 ± 3.7 days. The addition of ASA did not increase bleeding activity or the demand for transfusion. Relative changes of CO_2 removal on day 3 expressed as a percentage in the ASA group were (mean value) −11.8% in comparison with control (−3.0%, p = 0.266), but the relative amount of oxygen transfer tended to be increased in the ASA group (+3.9%) and to be decreased in the control group (−14.7%, p = 0.214). Pa_{O_2}/Fi_{O_2} ratio was significantly improved in the ASA group compared with the control group at day 5. The use of membranes per patient (membrane/patient ratio) tended to be decreased in patients treated with ASA (1.12 ± 0.34) in comparison with control (1.33 ± 0.62, p = 0.157). In the ASA group, one patient died due to multiple organ failure, whereas in the control group, five patients died. We conclude that supplementation of low-dose ASA during pumpless extracorporeal lung support is safe and might preserve the function of oxygen transfer. *ASAIO Journal* 2011; 57:164–168.

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Pump-driven extracorporeal membrane oxygenation (ECMO) or pumpless arterio-venous interventional lung assist (iLA) is used in cases of life-threatening severe hypoxemic/hypercapnic respiratory failure.[1–3] Advances in these techniques have reduced complication rates, and in a recent prospective randomized study, a reduction in mortality or severe disability was demonstrated in patients suffering from severe acute respiratory distress syndrome (ARDS) by the use of ECMO compared with patients managed by conventional mechanical ventilation.[4] Although similar reports on improved survival with iLA are lacking, there are investigations on the beneficial effects of iLA on the extracorporeal removal of CO_2 or the increase in arterial oxygenation.[3,5] In contrast to ECMO, iLA is a single-use ultracompact extrapulmonary gas-exchange system perfused by the heart. A passive femo-femoral shunt flow generated by the arterial blood pressure through a lung assist device (Novalung GmbH, Talheim, Germany) produces a blood flow rate of approximately 1 L/min. Both ECMO and iLA are associated with possible complications, with frequencies ranging from 20% to 50%.[3,6] The principal causes of complications are bleeding and thrombosis due to contact of the cellular components of the blood with the "non-biologic" surface of extracorporeal circuits, resulting in inflammatory and clotting responses.[7] For the prevention of clotting and thrombosis, the surface of extracorporeal circuits and gas-exchange systems is coated with heparin, and the additional continuous infusion of heparin is advocated. Despite this anticoagulation management, the formation of clots resulting in increased resistance to blood flow is observed during iLA use. We reported that additional application of acetylsalicylic acid (ASA) in a patient treated with iLA for acute lung failure was helpful when a marked drop in blood flow rate in the extracorporeal system was observed despite adequate anticoagulation with heparin.[8]

In this prospective cohort study, we report our experiences with the additional use of low-dose ASA with heparin to prevent clotting activity. Our hypothesis was that this new anticoagulation management would help to prevent thrombosis without increasing bleeding complications.

Materials and Methods

Between December 2008 and January 2010, iLA was implemented in 15 patients suffering from severe respiratory failure (**Table 1**), and ASA was added to heparin for anticoagulation. The concept of evaluation, insertion, and clinical

monitoring of iLA has been described in detail elsewhere.[3] In brief, cannulae were inserted using Seldinger's technique in the femoral artery and in the contralateral femoral vein by experienced physicians. After connection of the gas-exchange membrane to the cannulae, the shunt flow was released and controlled continuously by transit time Doppler technology (Sono TT ultrasonic flowmeter, em-tec GmbH, Finning, Germany). After insertion of the iLA-system, a de-escalation of invasive ventilatory variables (*i.e.*, tidal volume, inspiratory plateau pressure, frequency, and inspiratory fraction of oxygen) was performed to establish sufficient gas exchange by lung protective ventilation. Mean arterial blood pressure (MAP) was measured continuously during extracorporeal treatment, and volume and/or vasopressor agents were given to maintain MAP values ≥70 mm Hg.

The size of the arterial cannulation was individually selected to prevent ischemic complications of the lower limb: after ultrasonographic identification and assessment of the femoral artery and vein, an appropriately sized cannula that ensured sufficient peripheral blood flow (residual lumen ≥30%) was inserted. In most cases, the diameter of the arterial cannula was 15 French (Fr), whereas the venous cannula was selected to be 2 Fr larger, so that the flow resistance is not compromised. A continuous infusion of heparin ([Heparin-Natrium-25,000, Ratiopharm, Ulm, Germany] 200–600 IU/h) was given into the arterial cannula before the gas-exchange membrane to achieve a mild prolongation of the partial thromboplastin time (PTT ≈ 50 seconds). In addition, ASA (Aspisol, Bayer Vital, Germany) was administered intravenously after initiation of iLA with a dosage of 1.5 mg/kg actual body weight/d. We decided to apply ASA intravenously and not orally because critically ill patients often present with disturbed intestinal function and altered gastrointestinal motility and/or resorption capacity. The necessity for change of the artificial membrane was seen in situations, in which a marked reduction in iLA blood flow was observed (<0.9 L/min) despite hemodynamic stability (MAP ≥70 mm Hg) and without evidence for other reasons of reduced flow (kinking of cannula, etc.).

Two patients with acute bleeding problems (PTT >60 seconds and/or platelet count <60,000) and one patient with severe brain injury (Glasgow Coma Scale Score <9 and/or pathologic brain computed tomography scan) were excluded from ASA application. One patient with a suspected diagnosis of heparin-induced thrombocytopenia (HIT) was supplied with iLA but was excluded from the present analysis. Patients suffering from acute shock syndrome (norepinephrine infusion >0.4 μg/kg/min to maintain MAP ≥70 mm Hg) were excluded from iLA treatment and were, in cases of life-threatening hypoxemia/hypercapnia, connected to pump-driven ECMO. The transfusion of blood components followed our institution's policy aimed at ensuring a hemoglobin level of ≥9 g/dl, whereas fresh-frozen plasma was given in cases of active bleeding and/or a prothrombin time-international normalized ratio (PT-INR) >1.2. Platelets were transfused in situations of platelet blood levels below 60,000 counts/μl.

During iLA treatment, changes in coagulation parameters, free hemoglobin levels, the demand for transfusion of blood components, and hemodynamic variables were documented. Furthermore, we compared the function of the artificial membranes (oxygen transfer and capacity of CO_2 removal) of the

Table 1. Characteristics of Patients Treated with Interventional Lung Assist and Anticoagulation Management Including Acetylsalicylic Acid and Heparin (ASA Group) and in the Matched-Pair Control Group (CON) Treated with Heparin Alone

Diagnosis Leading to Acute Respiratory Distress Syndrome	ASA Group, No. (%)	Control Group, No. (%)
Trauma	7 (47)	6 (40)
Pneumonia caused by bacteria	3 (20)	7 (47)
Sepsis	3 (20)	2 (13)
Aspiration, toxic inhalation	2 (13)	

Table 2. Severity of Disease and Duration of iLA Treatment in Patients Treated with Acetylsalicylic Acid (ASA Group) and in the Matched-Pair Control Group (CON Group)

	ASA Group	Control Group
Age (yr)	47 ± 8	47 ± 6
Male	13	13
SOFA score	8.1 ± 2.9	9.7 ± 1.9
SAPS-II score	34.2 ± 10.6	41.1 ± 9.5
Initial Pao_2/Fio_2 ratio	152 ± 38	102 ± 61
Lung injury score (Murray)	3.1 ± 0.3	3,3 ± 0.5
Days on iLA	6.6 ± 3.7	9.6 ± 7.1

iLA, interventional lung assist; SOFA, Sequential Organ Failure Assessment; SAPS, Simplified Acute Physiology Score.

Table 3. Changes in Coagulation Parameters, Hemoglobin, and Free Hemoglobin Level Before, During, and After iLA Treatment in Patients Treated with Acetylsalicylic Acid (ASA Group) and in the Matched-Pair Control Group (CON Group)

	ASA Before iLA	CON Before iLA	ASA-T_{24}	CON-T_{24}	ASA-T_{72}	CON-T_{72}	ASA After Removal of iLA	CON After Removal of iLA
Platelet count/μl	188 ± 72	220 ± 160	204 ± 54	191 ± 154	216 ± 55	161 ± 86	308 ± 112*†‡	164 ± 51§
PT-INR	1.19 ± 0.13	1.23 ± 0.34	1.12 ± 0.13	1.21 ± 0.21	1.11 ± 0.13*	1.24 ± 0.19	1.20 ± 0.36	1.22 ± 0.28
PTT (s)	43.5 ± 7	55.9 ± 34	44.6 ± 10	52.3 ± 13	51.2 ± 11	59.2 ± 21*	37.9 ± 7	50.1 ± 17
Hb (g/dl)	9.9 ± 2.2	10.9 ± 2.9	10.2 ± 2.1	11.9 ± 5.4	9.5 ± 1.7†	10.2 ± 1.7		9.4 ± 1
Free Hb (mg/dl)	71 ± 42				81 ± 57			70 ± 44

Data are presented as mean values ± SD. T_{24}, T_{72} = 24 h, 72 h after initiation of iLA.
*$p < 0.05$ in comparison with "Before iLA."
†$p < 0.05$ in comparison with "T_{24}."
‡$p < 0.05$ in comparison with "T_{72}."
§$p < 0.05$ between groups.
iLA, interventional lung assist; PT-INR, prothrombin time-international normalized ratio; PTT, partial thromboplastin time; Hb, hemoglobin.

Table 4. Acetylsalicylic Acid (ASA), Heparin Application Dosages (Mean Values ± SD), and Demand for Transfusion of Blood Components in Patients Treated with Acetylsalicylic Acid (ASA Group) and in the Matched-Pair Control Group (CON Group; Median and Min–Max Values)

	ASA Group	CON Group
ASA total dosage (mg)	687 ± 268	—
ASA per iLA day (mg)	119 ± 61	—
Heparin total dosage (IU)	84,700 ± 2,600	144,300 ± 8,800*
Heparin per iLA day (IU)	11,350 ± 1,800	13,650 ± 2,700*
Units of RBC transfused	0 (0–7)	2 (0–4)*
Units of FFP transfused	0 (0–2)	1 (0–2)
Units of platelets transfused	0 (0–3)	0 (0–1)

*$p < 0.05$ between groups.
iLA, interventional lung assist; RBC, red blood cells; FFP, fresh-frozen plasma.

ASA group with that of a matched-pair control group (gender, diagnosis, age, and severity of disease) treated with heparin alone, which was drawn from our retrospective analysis in 90 patients with no ASA application.[3] Our institutional review board denied the necessity for approval to publicize the data.

The statistical analysis was performed using SPSS software, version 18.0 (SPSS Inc., Chicago, IL). Most datasets are presented as means and standard deviations. Some datasets significantly varied from the pattern expected if they were drawn from a normal distribution, as revealed by the Kolmogorov-Smirnov method, and are presented as median and min-max values. Significance was analyzed by the Wilcoxon Signed Rank Test (intragroup analysis). Results were considered significant at $p < 0.05$.

Results

All patients suffered from severe lung injury as assessed by Lung Injury Score and presented with general critical illness (**Table 2**). The mean duration of iLA treatment was 6.6 ± 3.7 days, and patients were mechanically ventilated for 14.3 ± 9.7 days. One patient died during hospital treatment due to multiple organ failure.

We found a significant increase in platelet count during iLA treatment, whereas other coagulation parameters remained stable. The hemoglobin level showed a moderate but statistically significant reduction on the 3rd day after initiation of iLA treatment (Table 3). The level of free hemoglobin was not reduced during iLA treatment and ASA application. The dosage of anticoagulation drugs required and the demand for blood transfusion are documented in **Table 4**. There was no increased bleeding activity or any demand for transfusion of red blood cell units, fresh-frozen plasma, or platelets resulting from ASA application in comparison with the matched-pair control group. Two examples of electron micrograph are presented in **Figure 1**, demonstrating iLA microfibers after the use of (**Figure 1A**) and without the addition of (**Figure 1B**) ASA. We saw no bleeding complications during or after the withdrawal of cannulae or in other organ systems. Hemodynamic variables are listed in **Table 5**. During iLA treatment and application of our combined anticoagulation management, the patients remained stable, and no increased demand for vasopressor infusion was noticed. iLA flow was significantly increased in the control group because of our former practice to use cannulae with a larger diameter (17 Fr) in comparison with our present practice (15 Fr). In addition, no transient ischemia was observed in the lower limb in which the femoral artery was cannulated.

Pulmonary gas exchange, and the amount of oxygen transfer and CO_2 removal immediately after implementation of iLA and on days 3 and 5 are demonstrated in **Table 6**. Pulmonary gas exchange was significantly reduced in the control group in comparison with the ASA group at day 5 after implementation of iLA. The amount of O_2 transfer tended to be increased during treatment in the ASA group but not in the control group. Relative changes of O_2 transfer and CO_2 removal expressed as a percentage on day 3 are shown in **Figure 2**. The relative changes of oxygen-transfer capacity were increased in the ASA group on day 3, but reduced in the control group, but for the

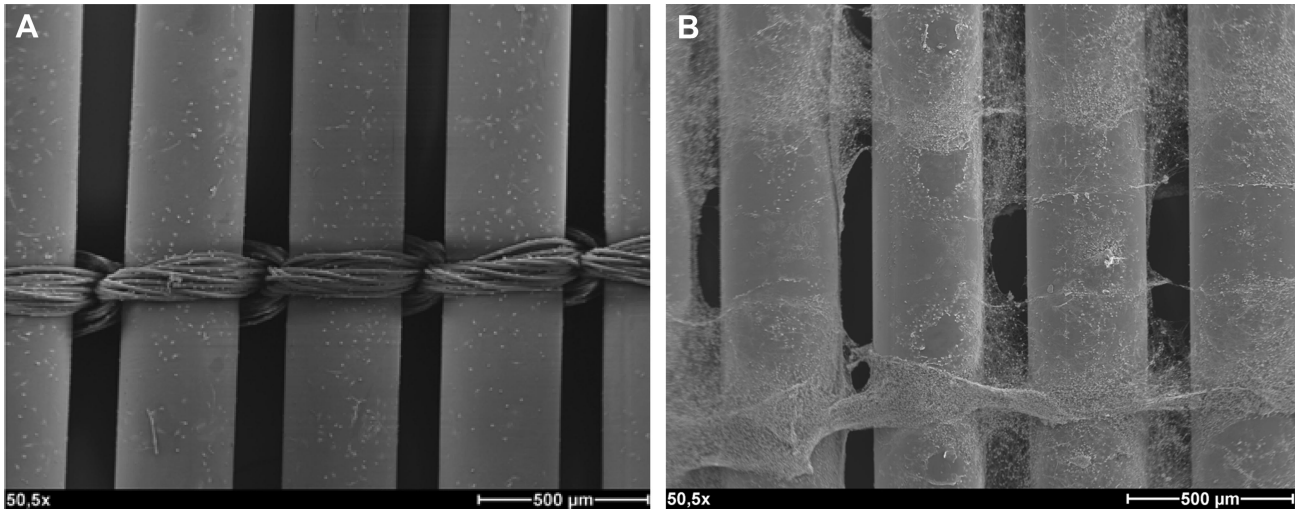

Figure 1. Electron-microscopic pictures of iLA microfibers (view on the outer surface of the fiber) after use with addition of ASA (**A**) and after use with application of heparin only (**B**). Note the beginning of fibrin net and clotting in (**B**). iLA, interventional lung assist; ASA, acetylsalicylic acid.

Table 5. Hemodynamic Variables and iLA Blood Flow in Patients Treated with Acetylsalicylic Acid (ASA Group) and in the Matched-Pair Control Group (CON Group)

	ASA Before iLA	CON Before iLA	ASA T_{24}	CON T_{24}	ASA T_{72}	CON-T_{72}	ASA After Removal of iLA	CON After Removal of iLA
MAP (mm Hg)	74 ± 10	72 ± 10	84 ± 13	86 ± 14	81 ± 11	81 ± 11	79 ± 8	87 ± 13
HR (bpm)	82 ± 18	84 ± 15	81 ± 16	85 ± 17	80 ± 13	79 ± 14	91 ± 24	97 ± 19
iLA flow (L/min)	—	—	1.4 ± 0.2	1.9 ± 0.3*	1.4 ± 0.18	1.6 ± 0.3	—	—

Data are presented as mean values ± SD. T_{24}, T_{72} = 24 h, 72 h after initiation of iLA.
*$p < 0.05$ between groups.
MAP, mean arterial pressure; HR, heart rate; iLA, interventional lung assist.

changes in CO_2 removal, we observed vice versa results. The use of membranes per patient (**Table 7**: membrane/patient ratio) tended to be decreased in patients treated with ASA (1.12 ± 0.34) in comparison with control (1.33 ± 0.62, $p = 0.157$). The incidence of iLA-associated complications was not different between groups. In the ASA group, one patient died due to multiple organ failure, whereas in the control group, five patients died, but initial SOFA and SAPS scores were higher in this group.

Discussion

Recent advances in novel techniques of extracorporeal lung support (miniaturization of pump-driven ECMO and pumpless extracorporeal lung assist[9]) have stimulated the integration of these measures in a clinical regime for the management of severe acute respiratory failure[10] aimed at providing adequate gas exchange and simultaneously allowing clinicians to prioritize lung-protective ventilation.

For both the ECMO and iLA systems, the extracorporeal gas-exchange membrane constitutes the core of the system, in which blood flows around bundles of gas-bearing hollow fibers with a large surface area. The gas exchange takes place at the boundary layer according to partial pressure gradients. With ECMO, the driving pressure is performed by a pump with a veno-venous cannulation, but the principle of iLA is the establishment of an arterio-venous pressure gradient in which the patient's heart acts as the pump. A common phenomenon of both techniques is the induction of an inflammatory and clotting response due to the contact of blood and its related components with the nonbiologic surface of the extracorporeal circuit. This response leads to the consumption and activation of procoagulant and anticoagulant components of cellular and noncellular cascades. In a recent autopsy series of ECMO patients, unexpectedly high rates of systemic thromboembolic events with an almost linear increase with duration of extracorporeal support (80% incidence after 10 days ECMO use) were found.[11] Therefore, adequate anticoagulation is crucial for the effective use of extracorporeal systems while, on the other hand, possibly increasing the risk of bleeding. Consequently, the goal of anticoagulation for extracorporeal lung support is to prevent thrombosis in the patient/technical device and prevent excessive bleeding. Current recommendations are based on the continuous infusion of heparin monitored by various coagulation parameters (*i.e.*, activated clotting time, PTT, and PT-INR.[7]).

Blood flow by a pumpless iLA device was identified as the main determinant of efficacy of oxygenation improvement and CO_2 elimination.[12] Conversely, it has been shown by electron and fluorescence microscopy that cellular deposits are frequently observed on the surface (polymethylpentene) of gas-exchange membranes, increasing the resistance to blood flow and affecting the gas-exchange capacity.[13]

We, therefore, decided to add an inhibitor of platelet aggregation to heparin, and in the present investigation, we present a feasibility study. The main results of our prospective cohort study are the following: 1) addition of ASA (1.5 mg/kg/d) does not increase the risk of bleeding or the amount of transfused blood components compared with "conventional" use of heparin alone; 2) laboratory values of coagulation parameters were unaffected by the addition of ASA to heparin in our patients; and 3) we found evidence that additional ASA preserved the amount of oxygen transfer through the membrane in comparison with a matched-pair group treated with heparin alone. Furthermore, we observed a trend for a lower membrane/patient ratio, which allows for a less necessity of changing the membrane.

Most of our patients were trauma patients suffering from severe posttraumatic ARDS due to direct or indirect involvement of the lung. Although it has been shown in a series of 28

Table 6. Pao_2/Fio_2-Ratio, $Paco_2$, and Amount of Transfer of Oxygen (O_2 Transfer) and Removal of Carbon Dioxide (CO_2 Removal) by the Membrane on Day 1 (Immediately After iLA-Implementation) and on Days 3 and 5 in Patients Treated with Acetylsalicylic Acid (ASA) and in the Matched-Pair Control Group (CON)

	ASA (Day 1)	ASA (Day 3)	ASA (Day 5)	CON (Day 1)	CON (Day 3)	CON (Day 5)
Pao_2/Fio_2	168 ± 40	177 ± 44	180 ± 45	114 ± 42*	152 ± 72†	120 ± 62*
O_2 transfer (ml/min)	29 ± 13	31 ± 8	34 ± 13	55 ± 22†	41 ± 12	38 ± 15
$Paco_2$ (mm Hg)	55 ± 11	54 ± 13		69 ± 20	45 ± 8†	
CO_2 removal (ml/min)	145 ± 53	135 ± 31	138 ± 52	151 ± 38	149 ± 47	142 ± 43

*$p < 0.05$ between groups.
†$p < 0.05$ in comparison with day 1.

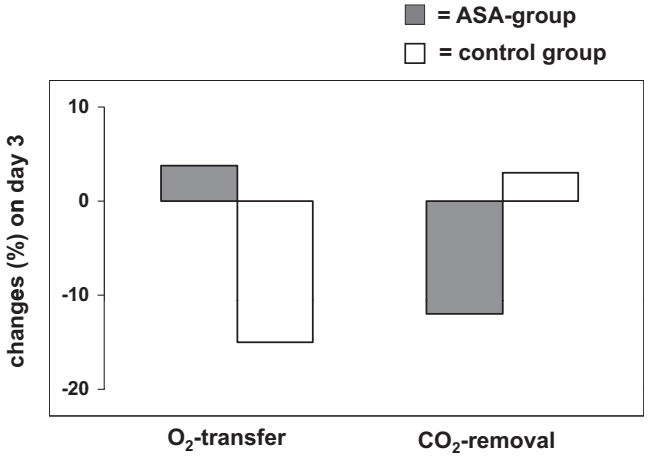

Figure 2. Relative changes of O_2 transfer and CO_2 removal through the membrane expressed as a percentage on day 3 compared with day 1 (immediately after implementation of iLA). ASA group = 15 patients treated with addition of low-dose acetylsalicylic acid to heparin for anticoagulation. CON group = 15 patients matched-pair controlled, treated with heparin alone. iLA, interventional lung assist; ASA, acetylsalicylic acid.

patients that extracorporeal life support has been safely used after trauma,[14] the indication for ECMO or iLA is critical in these patients because the risk for bleeding complications is high, and conversely, trauma is known to promptly induce coagulation cascades. The analysis of seven trauma patients in this study indicates that the use of low-dose ASA is safe and effective, but we do not recommend the use of ASA in patients with moderate-to-severe traumatic brain injury or severe preexisting coagulation disorder. The "ideal" anticoagulation management of patients on extracorporeal lung support should be studied in future experimental and clinical studies. We believe that the results of this study may impact additional investigations on the use of low-dose thrombocyte aggregation inhibitors to optimize anticoagulation without harming the patient.

Table 7. Days on iLA, the Amount of Membranes per Patient (Membrane/Patient Ratio), and the Incidence of Complications in Patients Treated with Acetylsalicylic Acid (ASA) and in the Matched-Pair Control Group (CON)

	ASA	Control (n = 15)	*p*
Days on iLA	6.6 ± 3.7	9.6 ± 7.1	0.083
Membrane-patient ratio	1.12 ± 0.34	1.33 ± 0.62	0.157
Complications	3/15 (20%)	3/15 (20%)	

iLA, interventional lung assist.

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