Wien Klin Wochenschr (2011) 123: 117–119
DOI 10.1007/s00508-010-1526-7

Printed in Austria

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Novel observations during extracorporeal membrane oxygenation in patients with ARDS due to the H1N1 pandemic influenza

Marko Kutleša, Marija Santini, Vladimir Krajinović, Dinko Raffanelli, Bruno Baršić

Department of Neuroinfections and Intensive Care Medicine, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb, Croatia

Received April 7, 2010, accepted after revision November 24, 2010, published online January 3, 2011

Neu beobachtete Phänomene während des Einsatzes der extracorporalen Membranoxygenation (ECMO) bei ARDS als Folge einer H1N1 pandemischen Influenza

Zusammenfassung. Wir berichten über neue Phänomene, die wir bei vier Patienten während des Einsatzes einer ECMO beobachtet haben. Die ECMO wurde wegen schwerem ARDS als Folge einer Pneumonie im Rahmen einer pandemischen Infektion mit H1N1 Influenza durchgeführt. Zwei Patienten hatten einen exzessiven Anstieg von konjugiertem Bilirubin im Serum. Die anderen zwei Patienten hatten einen unverhältnismäßigen Abfall des Gerinnungs Faktors IX. Die pathogenetischen Mechanismen und die klinische Bedeutung dieser beobachteten Phänomene werden diskutiert.

Summary. We report four patients with novel observations during extracorporeal membrane oxygenation support (ECMO). ECMO was initiated because of severe ARDS due to the primary H1N1 pandemic influenza pneumonia. Two patients had excessive conjugated hyperbilirubinemia and two had unproportional depletion of the coagulation factor IX. Pathogenetic mechanisms and clinical relevance of the noticed phenomena are discussed.

Key words: Extracorporeal membrane oxygenation, hyperbilirubinemia, factor IX, pandemic H1N1 influenza, cholestasis.

Introduction

Extracorporeal membrane oxygenation (ECMO) has emerged as an important treatment option for the severe ARDS, especially during the H1N1 influenza pandemic [1, 2]. The principal mode of ECMO used in this indication is veno-venous (VV-ECMO) and less commonly veno-arterial ECMO support (VA-ECMO) is applied. Even though VV-ECMO is a safer procedure than VA-ECMO both procedures are fraught with numerous complications. Description of these complications is beyond the scope of this manuscript.

During the recent influenza pandemic we had 10 ECMO procedures in 9 patients at our ICU. In those procedures we observed two repeating phenomena of possible clinical relevance that have not been reported in the literature thus far.

Two patients had excessive, predominantly conjugated hyperbilirubinemia without significant hepatic tissue damage or impaired hepatic synthetic function and with liver function tests that were indicative of cholestasis. Cholestasis during ECMO has been reported in neonates [3]. However, it has not been reported in adults and its severity in our patients is quite puzzling. The etiology of the disorder remained elusive despite the work-up conducted.

In two other patients, severe and isolated depletion of the coagulation factor IX occurred with possible connection to the clinically relevant bleeding as a consequence. The cause of the extreme factor IX depletion was not determined. However, it might be related to heparinisation and extracorporeal blood flow.

The possible pathogenic mechanisms and clinical relevance of the observed phenomena are discussed.

Patients

During the influenza pandemic between November 2009 and March 2010, our ICU started to treat severe ARDS patients with VV-ECMO support. Reported patients had proven primary influenza pneumonia with real-time polymerase chain reaction (Prodesse's ProFlu-ST™) from the tracheal aspirate and severe ARDS that required VV-ECMO support. While on ECMO, two patients had marked conjugated hyperbilirubinemia and two had unproportional depletion of coagulation factor IX. These compli-

Correspondence: Marko Kutleša, M.D., Department of Neuroinfections and Intensive Care Medicine, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Mirogojska 8, 10000 Zagreb, Croatia, E-mail: marko.kutlescha@gmail.com

cations during ECMO have not been reported in the literature thus far.

Patients with conjugated hyperbilirubinemia

A 33-year-old previously healthy male patient was admitted to our ICU because of severe ARDS. Gradual increase of the serum bilirubin was noted after three days of ECMO support. Bilirubin value peaked one day after the patient was weaned from ECMO and was 857.1 µmoles/L. Conjugated fraction was 597.9 and the unconjugated one was 259.2 µmoles/L. Aspartate aminotransferase (AST) peaked at 407 U/L, alanine aminotransferase (ALT) at 415 U/L, gamma-glutamyl transferase (GGT) was 177 and alkaline phosphatase (ALP) was 236 U/L. Lactate dehydrogenase (LDH) was 3067 U/L due to previous hemolysis. Serum amylase was within normal limits. At the time when serum concentration of bilirubin peaked prothrombin time (PT) was 71% and albumin was 42.1 g/L without albumin or fresh frozen plasma supplementation. Ultrasound of the liver and the biliary tract revealed only diffusely enlarged liver of 20 cm in the midclavicular line (MCL). At discharge two months later the patient had normal serum bilirubin as well as the liver function tests.

Second patient was a 23-year-old previously healthy female patient. She was pregnant for 24 weeks and was admitted to our ICU because of severe ARDS. Serum bilirubin concentration begun to increase significantly after five days. On the 9th day of the procedure serum bilirubin was 810.7 µmoles/L with the conjugated fraction of 558.8 µmoles/L. At that time AST was 173 U/L, GGT and ALP were 154 U/L and 212 respectively, ALT was within normal ranges. PT was 65% and albumin levels were normal without supplementation. Serum amylase was within normal limits. Ultrasound of the liver and the biliary tract revealed only diffusely enlarged liver of 24 cm in the MCL line. Bilirubin levels decreased gradually over the next days. However, the patient died of refractory respiratory failure one week after the serum bilirubin level reached its peak. Two days prior to the fatal outcome of the patient a stillborn fetus was delivered. Autopsy revealed that fetal death was due to ischemia (Table 1).

In both patients viral hepatitis A, B, and C were serologically excluded and cytomegalovirus and Epstein Barr virus infection were excluded by means of PCR.

Patients with severe depletion of factor IX

Both patients were admitted because of severe ARDS and hemophilia B was excluded with normal factor IX contentration prior to the ECMO procedure. The activated coagulation time (ACT) values were in the range between 160 and 180 seconds in both patients throughout the ECMO procedure. A 43-year-old male with the history of hypertrophic cardiomyopathy was weaned from ECMO after 6 days because the respiratory function improved sufficiently. Immediately after the weaning process was completed neurologic deterioration was noted and cerebral circulatory arrest was confirmed with transcranial doppler sonography. On the same day the activity of factor IX was less than 2% of normal and the activity of factors II, V, VII, VIII and X was within normal range. The autopsy revealed large intracerebral hematoma.

In the second patient, previously healthy 30-year-old male, we noticed severe factor IX depletion after 9 days of ECMO support. The measured activity of factor IX was 11% and the activity of the factors II, V; VII, VIII and X was normal. One day previous to the observed factor IX depletion significant hemorrhage from the trachea occurred. The patient was treated with purified human factor IX in the recommended doses immediately after the depletion was noticed. On the same day the hemorrhage from the trachea ceased. Eleven days after this episode the patient died in septic shock (Table 2).

Discussion

We report two novel observations occurring in adult patients on ECMO support. In two patients we noticed excessive conjugated hyperbilirubinemia and in two patients we observed severe factor IX depletion.

According to the nature of the hepatic injury and to the absence of any visible pathological process in the liver or biliary tract, the most plausible cause of conjugated hyperbilirubinemia in our patients is intrahepatic cholestasis. The etiology of the noticed disorder remains unclear. However, ischemic insult to the hepatic tissue might cause the damage to the small bile ducts with consequent obstruction to the bile outflow. Intrahepatic cholestasis of

Table 1. Relevant laboratory data in patients with hyperbilirubinemia

	Time in days after ECMO initiation							
	Patient 1				Patient 2			
	1	3	9	16	1	5	9	16
Bilirubin (µmol) (conjugated)	8.2 (3.5)	318.5 (214.6)	857.1 (597.9)	430.0 (344.3)	20.6 (12.1)	92.6 (44.7)	810.7 (558.8)	323.0 (168.8)
AST[1] (U/L)	57	140	407	158	21	46	173	41
ALT[2] (U/L)	98	90	415	107	13	18	33	22
GGT[3] (U/L)	70	60	117	97	43	41	154	40
ALP[4] (U/L)	126	110	236	216	54	68	212	101
LDH[5] (U/L)	167	487	3067	735	212	452	721	571
CRP[6] (mg/L)	107.2	148.4	114.5	95.6	106.5	102.9	117.6	221.4
RBC[7] (10^{12}/L)	4.15	3.62	3.41	3.33	3.19	3.92	3.03	3.90
Hgb[8] (g/dL)	13.5	13.3	11.8	11.3	10.0	12.3	10.3	12.3
PLT[9] (10^9/L)	165	157	94	164	217	95	108	191
WBC[10] (10^9/L)	12.1	15.9	17.7	11.7	13.7	10.8	8.5	5.8

[1]aspartate aminotransferase; [2]alanine aminotransferase; [3]gamma-glutamyl transferase; [4]alkaline phosphatase; [5]lactate dehydrogenase; [6]C-reactive protein; [7]red blood cell count; [8]hemoglobin; [9]platelets; [10]white blood cell count.

Table 2. Relevant laboratory data in patients with coagulation factor IX depletion

	Time in days after ECMO initiation					
	Patient 3			Patient 4		
	1	3	6	1	9	11
PT1 (≥70%)	90	88	83	81	78	91
APTT2 (seconds)	32	72	47	31	42	34
Factor II (0.70–1.20)[3]	1.20	1.15	1.25	0.76	0.90	0.85
Factor V (0.70–1.40)	1.40	1.35	1.40	1.80	1.30	1.40
Factor VII (0.70–1.20)	0.85	0.84	0.88	0.84	1.15	1.20
Factor VIII (0.70–1.50)	1.04	0.71	0.79	0.74	0.86	1.50
Factor IX (0.70–1.20)	0.92	0.30	<0.02	0.98	0.11	1.20
Factor X (0.70–1.20)	1.03	1.18	1.18	1.09	1.12	1.20
Platelets (10^9/L)	223	120	188	124	118	99

[1]prothrombin time; [2]activated partial thromboplastin time; [3]parenthesis – normal values of coagulation factors.

pregnancy in second reported patient is unlikely because the values of ALT and AST were nearly normal. Furthermore, the bilirubin decreased while the patient was still pregnant. Unconjugated portion of bilirubin was attributed to hemolysis. Completely reversible nature of this phenomenon is comforting even though its pathogenesis and etiology are unknown. This kind of severe hyperbilirubinemia is extremely worrisome for every clinician since it usually represents a preterminal event. However, one of our patients gradually and spontaneously recovered, while the other died of refractory respiratory failure after the serum bilirubin concentration was decreasing. Despite only limited experience, it seems that cholestatic pattern of hyperbilirubinemia during ECMO without the proportional elevation of transaminases as markers of hepatic tissue damage and with preserved hepatic synthetic function, represents only transitory disorder in bilirubin metabolism. Furthermore, despite the impressive values of the measured serum bilirubin in our patients, the clinical significance of this phenomenon on the patient's outcome seems to be irrelevant.

Severe and unproportional depletion of factor IX of the coagulation cascade was noticed in two patients. Pathogenetic mechanism and etiology of the observed disorder eluded us, but it could be related to the activation of the coagulation cascade by the extracorporeal blood flow. However, this mechanism does not explain why other coagulation factors remained within normal limits. Heparin is an indirect thrombin inhibitor which complexes with antithrombin, converting this circulating cofactor from a slow to a rapid inactivator of thrombin, factor Xa, and to a lesser extent, factors XIIa, XIa and IXa. Obviously, the effect of heparin solely does not explain the isolated depletion of factor IX, but it might be a contributing factor for the occurrence of this phenomenon. Factor IX depletion in the first patient was noticed on the same day when the fatal intracranial hemorrhage occurred and on the day the patient was successfully weaned from ECMO support. After this unfortunate incidence, we routinely measured the concentration of coagulation factors daily. The second patient developed severe tracheal hemorrhage when factor IX activity dropped to 11%. After the treatment with purified human factor IX the hemorrhage ceased. The two patients described indicate that observed unproportional depletion of factor IX is of possible clinical significance since it might contribute to the severity of hemorrhage in different organ systems during ECMO procedure. Especially because in both patients ACT values were in the desired range, that is between 160 and 180 seconds. Despite, our only limited experience it seems prudent to monitor the activity of all coagulation factors daily while patients receive ECMO support and to treat factor IX depletion if significant hemorrhage occurs or if its value drops below 30% of normal. The value of 30% is sufficient for the postoperative period and thus it might be during the ECMO support as well [4].

This influenza pandemic established ECMO respiratory support as the leading treatment option for refractory ARDS worldwide [1, 2]. Consequently, numerous ECMO procedures were performed that resulted in some novel experiences. The novel phenomena we noticed seem to be related to the ECMO procedure itself and have no association with specific influenza etiology of the ARDS.

We believe that our particular observations might improve monitoring and the outcome of the future patients on ECMO support.

Authors' contribution

All authors wrote, reviewed, and revised the article and approved the final version of the manuscript. Dr. Kutleša was primarily responsible for data collection and writing the manuscript.

Conflict of interest

There is no conflict of interest.

References

1. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators; Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA 2009;302:1888–95.
2. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009;374:1351–63.
3. Abbasi S, Stewart DL, Radmacher P, Adamkin D. Natural course of cholestasis in neonates on extracorporeal membrane oxygenation (ECMO): 10-year experience at a single institution. ASAIO J. 2008;54:436–8.
4. Hermans C, Altisent C, Batorova A, Chambost H, De Moerloose P, Karafoulidou A, et al. European Haemophilia Therapy Standardisation Board. Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations. Haemophilia 2009;15:639–5.