Austin Journal of Obstetrics and Gynecology

Open Access

Austin Publishing Group

Research Article

Application of in Vitro Membrane Pulmonary Oxygenation Technology (ECMO) in Neonatal Respiratory Failure

Liyu Li[1]; Jingguo Chen[1*]; Qiaoru Li[1]; Rukang Yuan[1]; Tingbo Wu[1]; Kaijun Zheng[1]; Wenjing Xu[1]; Yijuan Li[2]

[1]The Affiliated Zhongshan Hospital, Sun Yat-sen University, China

[2]The First Affiliated Hospital, Sun Yat-sen University, China

[*]**Corresponding author: Jingguo Chen**

The Affiliated Zhongshan Hospital, Sun Yat-sen University, Zhongshan, 528403, China.

Email: chenjingguo@126.com

Received: June 24, 2023

Accepted: July 26, 2023

Published: August 02, 2023

Abstract

Objective: To explore the application of Extracorporeal Membrane Oxygenation technology (ECMO) in neonatal respiratory failure and provide guidance for future ECMO technology for critically ill newborns.

Methods: Retrospective analysis of the basic data, ECMO support process, and long-term neurological development of nine children supported by ECMO at Zhongshan People's Hospital from January 2015 to August 2021.

Results: From January 2015 to August 2021, the number of admissions to the neonatal department of our hospital was 10,325, with 433 cases of neonatal respiratory failure, which was in line with ECMO support indication of 21 cases, of which 12 were non-ECMO groups and 12 were ECMO groups. In nine cases, the differences in sex, birth weight, gestational age, birth pattern, Apgar score, NCIS score, OI value, hospitalization days, mortality rate, and incidence of intracranial bleeding were not statistically significant ($P>0.05$). However, the average daily hospitalization cost for children in the ECMO group was significantly higher than that in the non-ECMO group, and the difference was statistically significant ($P<0.05$). ECMO after 12 h operation, arterial oxygen pressure, and intravenous oxygen saturation are substantially enhanced, while arterial carbon dioxide pressure oxygenation index is considerably reduced, with a statistically significant difference ($P<0.05$). ECMO preoperation survival group lactic acid (6.46±2.70) was lower than the death group (17.66±14.62), after operation lactic acid decreased significantly, and after ECMO operation of the death group lactic acid showed an increase in conductivity. During the early stage of ECMO establishment, PT and APTT rapidly rise, while FIB decline. The ACT of both groups of children increased in the early stages of ECMO establishment and then gradually declined. In the ECMO group, seven children survived to discharge, six had no neurological developmental problems, and one had residual neurological sequelae.

Conclusion: ECMO can be employed as a complementary supportive treatment for newborns with respiratory failure, and the oxygenation condition can be effectively improved for newborns with respiratory failure who have failed to respond to traditional treatment.

Keywords: Newborns; Respiratory failure; In vitro membrane pulmonary oxygenation technology

Citation: Li L, Chen J, Li Q, Yuan R, Wu T, et al. Application of in Vitro Membrane Pulmonary Oxygenation Technology (ECMO) in Neonatal Respiratory Failure. Austin J Obstet Gynecol. 2023; 10(2): 1220.

Introduction

Extracorporeal Pulmonary Oxygenation (ECMO) is advanced in vitro life support system. However, the development of ECMO in China has been late and slow, with a modest number of clinical cases due to china's economic growth (Faith, 2020). In 2011, Guangdong was the first to report the use of ECMO to treat a case of fetus fecal inhalation syndrome of newborns and then ECMO technology in the domestic treatment of newborns. As of January 2019, China's ECMO technology had been applied to 89 newborns, with 33 cases (37.1%) of respiratory support, 43 cases (48.3%) of circulatory support, with survival rates of 66.7% and 37.2%, respectively [6]. Since January 2015, the Neonatal Unit of Zhongshan People's Hospital has used ECMO for neonatal care and treated a total of nine critically ill newborns by August 2021. This study retrospectively examines the critical respiratory failure newborns treated by ECMO technology, collects basic data, analyzes the treatment process and complications, and follows up with the neurodevelopment of discharged children. It also serves as a reference for future application of ECMO technology in critically ill newborns.

Data and Methods

Research Object Statistics

From January 2015 to August 2021, the number of cases diagnosed as neonatal respiratory failure in the neonatal department of Zhongshan People's Hospital, collects basic information on children who require ECMO support, and divides them into ECMO and non-ECMO groups based on whether or not ECMO support is needed. The non-ECMO group used ventilator and/or PS therapy to evaluate case data from both groups retrospectively.

Data Collection

We collected the general data on the two groups of children, including the gestational age, sex, birth weight, birth score, and compare the complications, mortality rate, hospital stay days, and medical expenses. Focused on the analysis of ECMO group children's auxiliary methods, diagnosis, and treatment process, and follow up the nervous system development of the ECMO group of surviving children.

Statistical Methods

All collected data are analyzed using SPSS 20.0 statistical software. The measurement data were normally tested by Shapiro-Wilk, the mean ± standard deviation of the normal distribution data, and the t-test was used to inter-group comparison. Non-normal distribution measurements are represented by the median (quartile spacing), while intergroup comparisons are measured using the Mann-Whitney U. The count data are described in frequency and percentage.

Results

General Information

From January 2015 to August 2021, the number of admissions to the neonatal department of our hospital was 10,325, with 433 cases (4.2%) of neonatal respiratory failure diagnosed, in line with the ECMO support index of 21 cases (0.2%). Fourteen (68.4%) were diagnosed with ARDS, whereas seven (31.8%) were diagnosed with Meconium Aspiration Syndrome (MAS).

In 12 cases the signatures had rejected the ECMO support due to economic conditions, including the non-ECMO group, and in nine cases signatures had agreed to ECMO support and were included in the ECMO group. In the non-ECMO group, there were 12 cases, with eight cases of men (66.7%) and four cases of women (33.3%). The average gestational age was 37 weeks, ranging from 34 weeks to 2 – 40 weeks to 4 weeks. The average birth weight was 2,680 g, ranging from 2,020 g to 3,560 g, with eight survivors (66.7%) and four deaths (33.3%). The ECMO group has nine cases, five cases for men (55.6%) and four cases for women (44.4%). The average gestational age was 38 weeks, ranging from 34 weeks to 3 to 40 plus 5 weeks. The average birth weight was 2,887 g, with a range of 2,130 g – 3,580 g with seven survived discharges (77.8%) and two deaths (22.2%). The differences in sex, birth weight, gestational age, birth pattern, NCIS score, OI value, number of days in the hospital, and incidence of intracranial bleeding were not statistically significant (P>0.05). The average hospitalization cost for children in the ECMO group was significantly higher than for children in the non-ECMO group, and the difference was statistically significant (P<0.05).

Changes in Laboratory Indicators in the Operation of ECMO

Changes in oxygenation indicators: Nine cases of ECMO in children after the establishment of 12 h arterial blood pressure divider (PaO2) with intravenous oxygen saturation (SaO2) were significantly higher than before, and arterial carbon dioxide pressure (PaCO2) and Oxygen Index (OI) were substantially lower than before, with statistically significant differences (P<0.05).

Changes in lactic acid values in ECMO operation: The survival group lactic acid before ECMO runs (6.46±2.70) was lower than lactic acid in the death group (17.66±14.62). However, after ECMO operation, the survival group lactic acid substantially reduced, while the death group lactic acid did not decrease significantly and increased in conductivity.

Table 1: Comparison of basic data for the two groups of children.

	ECMO group	non-ECMO group	t/z value	p
Sex (men/wemen)	5/4	8/4	0.394	>0.05
Gestational age (d)	266.86±16.59	259.33±15.08	1.012	>0.05
Birth weight (kg)	2.89±0.47	2.69±0.43	0.985	>0.05
Birth pattern (caesarean birth / eutocia)	4/5	5/7	-0.048	>0.05
NCIS score	76.26±6.68	72.33±5.31	1.425	>0.05
Apgar score				
1 min	7.0 (6,10)	8.5 (5.5,9)	-0.365	>0.05
5 min	8.0 (7,10)	9.5 (7.25,10)	-1.308	>0.05
OI value	70.71±6.02	66.92±5.58	1.391	>0.05
Hospitalizationcost (yuan/d)	5764.58 (4637.12,25129.47)	2696.28 (2299.19,4892.05)	1.683	<0.05
Hospital time (d)				
Survival rate (death / survival)	21 (3,32)	26.5 (2,32)	-0.213	>0.05
Complication (intracranial bleeding)	2/7	4/8	-0.204	>0.05
	4/9	2/12	0986	>0.05

Table 2: Comparison of 12h oxygenation indicators before and after ECMO establishment.

Time	PaO2	SaO2	PaCO2	OI
before ECMO	32.1±3.34	27.43±4.12	83.29±4.15	70.71±6.02
12h after ECMO	84.±10.95	95.00±4.93	40.57±4.86	14.71±6.10
t/z	-12.082	-27.824	17.680	17.286
p	<0.05	<0.05	0.001	<0.05

Table 3: Lactic acid changes after ECMO operation.

Time (h) / Num	0	1	6	12	18	24	48	72	96	120	144	168	192
Survival Group													
2	8.34	13.45	8.38	5.37	2.28	3.34	withdraw						
3	3.92	3.47	3.09	3.07	1.57	1.06	0.92	withdraw					
4	3.29	2.98	2.12	1.78	1.13	1.01	1.29	withdraw					
6	7.41	3.25	2.64	1.89	1.72	1.53	1.24	1.07	0.94	0.52	0.21	0.43	withdraw
7	9.34	4.72	3.97	2.31	1.78	1.03	0.59	0.33	withdraw				
8	8.63	7.52	7.21	6.53	3.25	1.27	0.35	withdraw					
9	9.57	13.54	10.85	8.63	8.21	7.24	6.23	5.24	2.87	0.45		withdraw	
Death group													
1	7.32	15.34	16.23	22.16	22.32	-	-	-	-	-	-	-	-
5	28	23.45	33.61	30	32	36.7	-	-	-	-	-	-	-

Table 4: Change of plasma clotting enzyme original time (PT/s) after ECMO runs.

Time (h) / Num	0	1	6	12	18	24	48	72	96	120	144	168	192
Survival group													
2	15	66.7	75.3	41.6	12.4	11.4	withdraw						
3	29.8	73.8	62.4	32.4	13.5	14.7	12.9	withdraw					
4	23.2	89.7	62.3	42.8	23.2	12.3	10.6	withdraw					
6	17.4	54.9	64.9	54.1	13.9	12.8	15.84	13.96	12.5	15.28	13.6	10.6	withdraw
7	34.2	65.8	50.4	48.1	13.4	13.8	11.1	12.3	withdraw				
8	38.6	78.2	65.8	43.2	38.2	28.1	12.5	withdraw					
9	40.5	89.5	78.5	70.5	65.2	52.7	42.5	31.5	28.4	12.5	withdraw		
Death group													
1	35.1	70.5	68.8	76.6	78.3	-	-	-	-	-	-	-	-
5	27.8	108	72.9	96.1	102.7	96.5	-	-	-	-	-	-	-

Table 5: Change of Activation of part of the clotting enzyme time (APTT/s) after ECMO runs.

Time (h) / Num	0	1	6	12	18	24	48	72	96	120	144	168	192
Survival group													
2	46.5	113.4	53.7	37.2	20.1	12.7	withdraw						
3	35.4	98.2	53.7	64.2	56.7	30.5	12.2	withdraw					
4	32	152.3	50.6	59.1	50.3	45.2	20.1	withdraw					
6	54	129	106.3	126.2	116.3	50.6	53.1	45.7	49.2	29.4	26.1	13.2	withdraw
7	21	107	87	54.3	38.3	39	25.3	10.3	withdraw				
8	35	125	112	85	53.8	25.6	15.2	withdraw					
9	46	132	124	105.6	85.4	65.5	52.6	47.8	32.7	12.5	withdraw		
Death group													
1	52.2	107	111.5	98.3	100.2	-	-	-	-	-	-	-	-
5	27.8	108	82.9	96.1	102.7	96.5	-	-	-	-	-	-	-

Table 6: Change of Activation of Fibrinogen (FIB/g/L) after ECMO runs.

Time (h) / Num	0	1	6	12	18	24	48	72	96	120	144	168	192
Survival group													
2	1.7	1.33	2.35	2.48	2.12	2.7	withdraw						
3	1.98	1.3	1.14	1.87	2.3	1.24	2.14	withdraw					
4	1.35	0.96	1.19	1.56	1.59	2.47	2.1	withdraw					
6	2.11	0.52	1.87	1.55	2.35	3.88	3.58	2.68	2.57	1.69	2.84	2.11	withdraw
7	2.68	0.98	1.41	0.95	1.09	0.87	0.84	1.61	withdraw				
8	1.85	1.02	2.31	2.57	2.65	3.02	2.01	withdraw					
9	1.65	1.06	2.41	2.68	3.52	3.96	2.23	2.02	1.96	1.53	withdraw		
Death group													
1	2.47	0.68	0.89	1.12	1.47	-	-	-	-	-	-	-	-
5	3.8	0.97	1.9	3.1	2.7	6.5	-	-	-	-	-	-	-

Table 7: Change of Activation of the clotting enzyme time (ACT/s) after ECMO runs.

Time (h) / Num	0	1	6	12	18	24	48	72	96	120	144	168	192
Survival group													
2	176	245	233	197	214	175	withdraw						
3	154	276	249	200	204	193	164	withdraw					
4	184	201	224	196	206	195	184	withdraw					
6	167	199	201	235	226	218	198	204	194	185	182	179	withdraw
7	186	194	187	194	167	183	185	174	withdraw				
8	153	251	203	185	175	170	169	withdraw					
9	186	298	276	245	217	186	174	173	167	162	withdraw		
Death group													
1	186	276	230	219	203	-	-	-	-	-	-	-	-
5	219	254	207	195	234	245	-	-	-	-	-	-	-

Changes in the function indicator of clotting during ECMO operation (Table 4 – Table 7): ECMO is established after the child's clotting enzymes, Prothrombin Time (PT), and Activated Partial Thromboplastin Time (APTT) are quickly elevated. Through blood plasma infusion, adjustment is made to the gradual decrease in the amount of heparin. Fibrinogen (FIB) and Platelet count (PLT) decline in the early stages of ECMO establishment, but infusions of FIB, PLT, and ECMO begin to rise once the system is stabilized. Activated clotting time (ACT) at the beginning of ECMO establishment, they all increased with the adjustment of heparin dosage, ACT decrease by degree. The survival group stabilized at 160 – 200S after ECMO-assisted 24 h.

Neurological Development in Surviving Children in the ECMO Group

The ECMO group had seven children who survived discharge, five were followed up for more than one year, and two were tracked until May. Five cases after discharge one-month outpatient check brain MRI, two cases suggest neonatal ischemic isoxyoxic encephalopathy (HIF), three cases suggest a small amount of cobweb sub-cavity bleeding, after reviewing the cranial brain MRI prompt lesions absorption, growth, and development similar to the same age children, no residual neurological sequelae. One case of ECMO evacuation after one week to check the cranial brain, MRI prompts the two-sided top pillow under the epidural, a little bleeding under the small brain screen, the left forehead scalp under the huge hematoma, during the hospital by pediatric surgery consultation scalp hematoma puncture extraction after the scalp hematoma reduced recovery. One month after discharge from the hospital, an outpatient review of cranial brain MRI revealed the left frontal cortex missing the residual obsolete hematoma, and the left temporal lobe was considered to have micro-bleeding or iron-containing hemoglobin composure. Children found not to rise in April, with mental movement stunting for more than half a month, grew and developed similarly to children of the same age after receiving the regular exercise rehabilitation treatment at our hospital. In one case after discharge, a one-month outpatient cranial brain MRI showed left basal section softening with brain atrophy. The child is now three years old, with a stable language development; however, this child can only pronounce monophonic words, such as mom and dad, but cannot express their own ideas. The child's sports development is stable; they can sit and stand on their own, but cannot walk, leaving neurological sequelae behind.

Discussion

Incidence of a Disease and Morbidity

Since 1976, when Robert Bartlett reported that ECMO was used to treat 13 critically ill newborns, ECMO has gradually been utilized to treat critical clinical conditions, and over 40,000 critically ill newborns have been treated with it. By January 2019, ELSO reported 41,701 severely ill newborns worldwide using ECMO therapy, accounting for 36.1% of the ECMO registrations, with a survival rate of about 66%. The ECMO in China now reports 89 cases of treatment of newborns, accounting for 2.3% of all cases [2]. Although domestic ECMO started late, and the number of studies on neonatal ECMO has reported fewer cases, the current reported number of neonatal samples is 33 cases, with the total survival rate of 52% [2]. The incidence of respiratory failure in newborns in this unit is about 4.2%, which is lower than reported at home and abroad [4,14]. The survival rate of children in the ECMO group was higher than that of the non-ECMO group in this study, but the difference was not statistically significant, and the analysis may be related to the neonatal cases of the unit. Due to the small number of cases included in the study and the use of ECMO for invasive operations, cost, and other factors, some of the ECMO-assisted children's families signed a request for conservative treatment, so that the number of cases included in the study is small, and hence the survival rate is relatively high. It is hoped that more research will continue to be increased in the later stages to increase the number of clinical cases.

The clotting indicator ECMO line is a foreign body relative to the human body. Blood contact with exogenous foreign bodies easily activates the human blood clotting system, so ECMO during the operation of the conventional use of heparin anticoagulant [7]. ACT is often used in clinical settings to assess heparinization, while small dose heparin pumps are used to maintain ACT at 160 – 200S. According to the findings of this study, the ACT value of two groups of children increased when ECMO was established, and the ACT value progressively stabilized with the adjustment of heparin dosage. The ACT value of children in the survival group stabilized at 24 h after ECMO was established and was generally maintained at 160 – 200S, with the amount of heparin was adjusted based on the ACT value after ECMO operation in the death group. However, the ACT failed to adjust to a safe level, and the analysis may be related to the child's severe clotting dysfunction caused by the whole-body infection. Therefore, ECMO should monitor the ACT every 1 – 2 h during operation and promptly adjust the amount of heparin. According to the ACT to remain within the standard range. Fibrinogen (FIB) is initially reduced in ECMO due to the activation of the clotting system after blood interaction with foreign bodies, the high consumption of fibrin, and the dilution of blood pre-charging. However, as the cell and protein compositions activated and promoted each other, finally the clotting-anticoagulant balance

tend to promote coagulation system, FIB gradually increased [3], this study also confirmed this, FIB in ECMO established an initial decrease, to ECMO operation after 6 h began to rise, FIB increased suggests that the blood is in a high coagulation state, and ECMO during the operation of the use of heparin anticoagulant, further promote the blood in a high coagulation state. Therefore, ECMO operation must maintain a balance of clotting function, prevent blood clots and bleeding, and reduce the formation of complications [11].

Changes in lactic acid: Several adult studies have shown that hyperlactic acidemia prior to ECMO suggests that patients have a higher risk of death. Furthermore, the changes in lactic acid values after ECMO operation are also prognostic factors affecting ECMO [8]. This study shows that pre-run lactic acid values (6.1) in the ECMO survival group 46±2.70) were lower than that of the death group (17.66±14.62), and the lactic acid value decreased substantially after operation. However, the lactic acid value decreased significantly after the ECMO operation of the death group and showed an increase in conductivity. The analysis may be related to persistent hypoxemia and low perfusion status. Lactic acid is a byproduct of anaerobic respiratory metabolism in cells, and its concentration of lactic acid reflects the body's tissue perfusion state and oxygen metabolism level [1]. Various causes lead to neonatal respiratory failure, body tissue cells in the hypoxia and low perfusion state, and an increase in blood lactic acid concentration. There is also literature showing that the concentration of lactic acid in the blood before ECMO was established was an independent predictor of mortality in Intensive Care Units (ICUs) [13]. Therefore, strictly grasp the ECMO applied to neonatal respiratory failure indications and contraindications at the same time, and closely monitor the changes in blood lactic acid levels, can be used as an indicator to judge the prognosis.

Long-term forward watch: Since ECMO is an invasive operation, and a range of nervous systems can be left behind. The mechanisms that cause neurological sequelae may be disrupted by the automatic regulation of the brain and the irregular flow of blood in the brain, and the damage to the brain may be caused by inflammatory reactions and their own immune responses (Ortega, 2019). Studies have shown that about 50% of children treated with ECMO leave behind varying degrees of neuro developmental abnormalities [12], with cognitive impairment being the most important. The hospital survived the discharge of seven cases of children, two cases of cranial brain MRI prompted newborn ischemic hypoxic encephalopathy (HIF), two cases suggested a small amount of cobweb sub-cavity bleeding, but the review of cranial brain MRI suggests that lesions have been basically absorbed, the current growth and development of children of the same age, no residual neurological sequelae, and literature reports do not match. In one case, ECMO evacuation after one week to check the brain MRI prompt intracranial bleeding, April was found not rising, and slow mental motor development slow for more than half a month. However, by the regular exercise rehabilitation treatment growth and development of my hospital is similar to that of children of the same age. One case of children discharged from the hospital one month after checking the brain MRI prompt left basal section softening with brain atrophy, the current child three-year-old, language development can pronounce monophonic and called father, mother and other simple repetitive words, cannot express their own ideas. The development of the child' motor development is stable, the child can sit and stand on their own, but cannot walk, leaving behind the after-effects of the nervous system. Active and effective neural motor intervention can improve the reduction of long-term neurological complications in children.

To sum up, ECMO is an effective treatment method for incurable respiratory failure in newborns, but there are many central nervous system complications. Furthermore, it is necessary to follow up the development of the nervous system closely and intervene in time to improve the prognosis.

References

1. Amodeo A, Erdil T, Vanetta C, Steigmiller K, Schmiady M, et al. Serum lactate at 24 hours is associated with outcome in children requiring extracorporeal membrane oxygenation for pulmonary causes – a retrospective, observational study. Swiss Med Wkly. 2020; 10: 150-1.
2. Bao Quan, Hong Xiaoyang, Liu Yingyue, etc. Analysis of the outcome of single-center pediatric in vitro membrane pulmonary oxygenation. Chinese Journal of Pediatrics. 2018; 56: 122-127.
3. Cartwright B, Bruce HM, Kershaw G, Cai N, Othman J, et al. Hemostasis, coagulation and thrombin in venoarterial and venovenous extracorporeal membrane oxygenation: the HECTIC study. Sci Rep. 2021; 11: 7975.
4. ELSO registry report: International summary. ECMO Registry of the Extracorporeal Life Support Organization (ELSO). Ann Arbor. 2018; 5: 45-48.
5. Kim F, Bernbaum J, Connelly J, et al. Survival and Developmental Outcomes of Neonates Treated with Extracorporeal Membrane Oxygenation: A 10-year Single Center Experience. J Pediatr. 2020; 10: 45-8.
6. Keebler ME, Haddad EV, Choi CW, McGrance S, Zalawadiya S, et al. Venoaaefial extracorporeal membrane oxygenation in cardiogenic shock. JACC Heart Fail. 2018; 6: 503-16.
7. Kruit N, Prusak M, Miller M, Barrett N, Richardson C, et al. Assessment of safety and bleeding risk in the use of extracorporeal membrane oxygenation for multitrauma patients:a multicenter review. Trauma Acute Care Surg. 2019; 6: 967-73.
8. Lin TT, Lin MH, Wu CK, Lin L, Lin J, et al. Early lactate changes improve the outcome prediction for extracorporeal membrane oxygenation. Eur J Cardio Thorac Surg. 2020; 58: 915-22.
9. Delin L, Yuguang W, Minna L, etc. Hemolactic acid assays assess the prognostic value of ECMO patients with psychogenic shock. Chin J Cardiovasc Surgery. 2019; 10: 101-5.
10. Ortega SB, Pandiyan P, Windsor J, Torres VO, Selvaraj UM, et al. A pilot study identifying brain-targeting adaptive immunity in pediatric extracorporeal membrane oxygenation patients with acquired brain injury. Crit Care Med. 2019; 47: e206-13.
11. Rama G, Middlesworth W, Neunert C, Streltsova S, Cheung EW. Antifactor Xa monitoring and hematologic complications of pediatric extracorporeal membrane oxygenation. ASAIO J. 2021; 67: 91-5.
12. Wien MA, Whitehead MT, Bulas D, Ridore M, Melbourne L, et al. Patterns of brain injury in newborns treated with extracorporeal membrane oxygenation. AJNR Am J Neuroradiol. 2017; 38: 820-6.
13. Yang L, Fan Y, Lin R. Blood lactate as a reliable marker for mortality of pediatric refractory cardiogenic shock requiring extracorporeal membrane oxygenation. Pediatr Cardiol. 2019; 40: 26-8.
14. Zhang L, Qiu Y, Yi B, Ni L, Zhang L, et al. Mortality of neonatal respiratory failure from Chinese northwest NICU network. J Matern Fetal Neonatal Med. 2017; 30: 2105-11.