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The Effect of Atrial Septal Defect in the Treatment of ARDS with Left Ventricular Dysfunction Simulating Severe COVID-19

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ABSTRACT

Objective: To explore the effect of atrial septal defect (ASD) and venoarterial extracorporeal membrane oxygenation (VA-ECMO) in the treatment of ARDS combined with left ventricular dysfunction (LVD) to find a new effective method for treating severe COVID-19 patients.

Materials and methods: Five large animal ARDS models of sheep were established by intravenous injection of Lipopolysaccharide. ASD was made under general anesthesia and VA-ECMO was simulated by extracorporeal circulation machine. The oxygenation of peripheral blood, systemic circulation, and cardiac function were observed under conditions of closed and opened ASD, and the significance of ASD shunt in improving cardiopulmonary function was evaluated.

Results: With ASD closed, the atrial shunts disappeared, the peripheral artery pressure of oxygen(PaO_2): 141.2±21.4mmHg, the oxygenation index (PaO_2/FiO_2): 353.0±53.5, the mean blood pressure (MAP): 49.3±13.5 mmHg, the heart was full; with ASD opened, the left-to-right shunt was observed, PaO_2: 169.3±18.9mmHg, PaO_2/FiO_2: 423.3±47.3, MAP: 68.2±16.1 mmHg, the range of cardiac motion significantly increased, heart beat was powerful, and systemic circulation significantly improved. Statistical analysis showed that there were significant differences between opened and closed ASD ($P < .01$).

Conclusion: ASD plus VA-ECMO is an effective method for the treatment of ARDS combined with LVD, which is the main cause of death in severe COVID-19 patients. However, further clinical validation is needed.

INTRODUCTION

The COVID-19 pandemic covered the globe in a few months. Mild to moderate cases of the disease can be cured by symptomatic treatment, and severe cases need a ventilator or even ECMO support [Ramanathan 2020]. The mortality of severe cases is up to 61.5% [Xiaobo 2020], the main cause of death is ARDS combined with pulmonary infection and circulatory failure [Zhou 2020]. Therefore, improving hypoxemia as well as heart function is the key point to reduce the mortality rate of COVID-19. VA-ECMO is one of the effective means to rescue patients with LVD [Franklin 2019]. However, conventional VA-ECMO cannot alleviate the problem of hypoxemia in the upper body, especially in the coronary artery [Kon 2017]. VAV-ECMO is difficult to control the flow of each pipeline. At the same time, the problem of left heart decompression cannot be solved well. It is the main cause of death for the patients with ARDS and LVD even with the support of VA-ECMO [Millar 2019]. Atrial septostomy creates a left to right channel by making ASD at the oval hole of the atrial septum, which is equivalent to the conventional left heart drainage after cardiac surgery. It is an effective way to promote cardiac recovery and improve the left heart function [Meuwese 2020]. It also has been successfully used in VA-ECMO to support patients waiting for heart transplantation [Dahdouh 2012]. However, this method has not been seen in the treatment of ARDS combined with LVD clinically or experimentally. We analyzed that ASD plus VA-ECMO can provide left to right shunt, which leads to: 1. Decompress the left heart and make it fully rest (another form of left cardiac drainage with less bleeding, infection, and other complications); 2. Improve pulmonary circulation, reduce pulmonary edema, and increase oxygen supply, especially for the coronary artery and brain; 3. Adjust the pressure between the left atrium and right atrium in real time, balance the blood volume between systemic and pulmonary circulation; all of the above contribute to increase the rescue success rate of ARDS with LVD or even total heart failure. Therefore, this study was designed to test the effect of VA-ECMO plus ASD on ARDS patients with LVD.

MATERIAL AND METHODS

The experimental animals: Five healthy adult sheep were selected as the experimental animals after examination by the Animal Ethics Committee of University of Chinese Academy of Sciences, according to the "Guide for the Care and Use of Laboratory Animals" (NIH publication 85-23, revised 1985). The animals were male and weighed 55±3.2 kg. We finished the experiment in the Leading Animal Experiment Center (Shenzhen), this center has the large animal experiment qualification.

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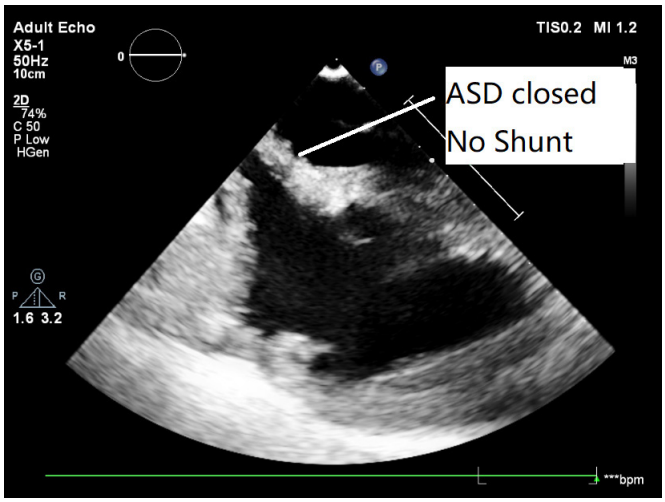

Figure 1. ASD closed with no shunt

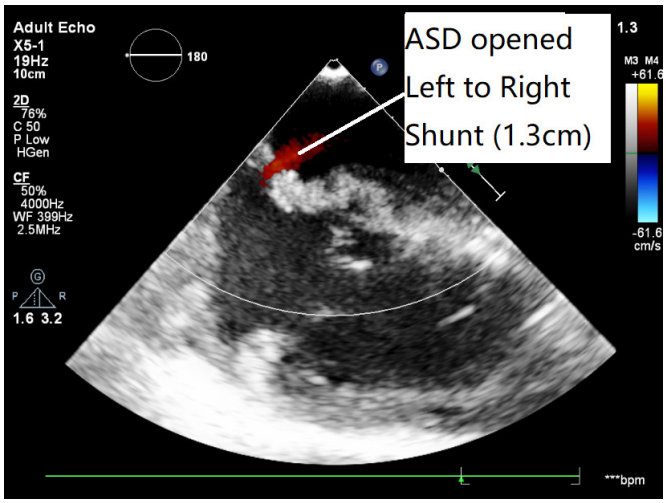

Figure 2. ASD opened with left to right shunt

Establishment of the animal model with ARDS: The pathological changes of COVID-19 in severe and terminal stage are ARDS, mainly with severe pulmonary edema and hyaline membrane in alveoli. Therefore, the animal model of ARDS can be used to simulate the pathological changes of COVID-19. The animal model was established by injecting intravenous infusion of Lipopolysacchatide (LPS) into the intubated sheep under general anesthesia. The animal model of lung injury produced by this method has been recognized internationally [Haitao 1999]. The dose of LPS was 3μg/kg, and severe lung injury could be induced within one hour, which reached the standard of ARDS ($PaO_2/FiO_2 \leq 300$mmHg).

Establishment of the animal model with LVD: After the establishment of the ARDS model, the right side of the chest was opened under the condition of obvious hypoxemia, the cardiopulmonary bypass (CPB) was established through the superior vena cava (SVC), inferior vena cava (IVC) and brachial artery (BA) intubation, the left atrial tube was placed through the right superior pulmonary vein, and ventricular fibrillation was induced after bypass started to cause myocardial injury depending on hypoxemia [Brann 2000].

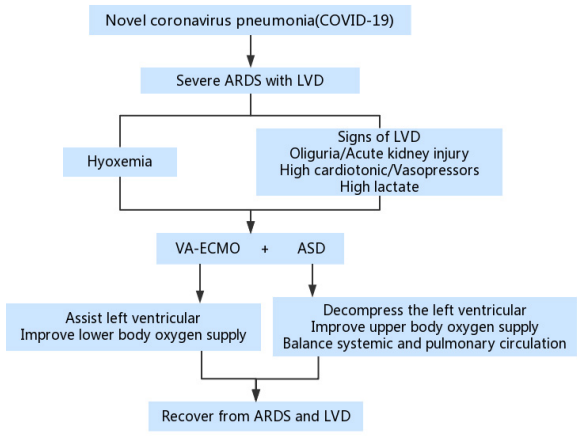

Figure 3. Mechanism diagram of VA-ECMO+ASD

Establishment of the animal model with ASD: After 20 minutes of ventricular fibrillation, we opened the right atrium, removed some septal membranous tissue roughly 1.5 cm in size, and applied a 2/0 sliptrack mattress suture on the edge of ASD to open or close ASD. After that, the right atrial incision was closed, and the operation was completed. We compared the changes of arterial parameters and hemodynamic index between the condition of ASD closed and ASD opened, with CPB simulating VA-ECMO.

Observation index: (1) General Index of animal hemodynamics; (2) Arterial Blood Gas Index and Mixed Venous Blood Gas Index; (3) Hemodynamics Index of systemic pulmonary circulation and change of lung water monitored by Pulmonary Artery Floating Catheter and PICCO; and (4) Esophageal and Epicardial UCG.

Statistical methods: Mean standard deviation and variance analysis were used, and SPSS 19 was used to process the data.

RESULTS

Animal model of ARDS: One hour after LPS injection, PaO_2: 198.3±37.2 mmHg, SaO_2: 93.1±1.3%, PaO_2/FiO_2: 198.3±37.2, HR: 87±17 beats/min, MAP: 61.5±13.2 mmHg (FiO2: 100%). The lung water significantly increased, the extravascular lung water index (ELWI) increased from 5.3±2.1 to 14.1±5.6 ml/kg, and the pulmonary vascular permeability index (PVPI) increased from 2.3±1.1 to 6.4±1.9, which means that the models of ARDS were successful.

Animal mode of ASD and LVD: The diameter of ASD was 12±2.1 mm (measured intraoperatively). After heart defibrillation and restarting, 30 minutes of parallel circulation with ASD closed was observed. The heart was in a weak and peristaltic state, indicating that the myocardium was severely damaged. After half an hour, the heart was still too weak to stop CPB, which indicated LVD.

Table 1. Changes of general parameters before and after ASD opened

Group	HR (beats/min)	MAP* mmHg	PAP* mmHg	LAP** mmHg	RAP mmHg
Opened ASD	98±18	68.2±16.1	18.1±7.8	11.4±2.1	10.2±3.6
Closed ASD	108±17	49.3±13.5	28.9±12.7	13.6±3.3	12.5±3.3
P-value	.1290	.0016	.0090	.0380	.0788

HR: heart rate, MAP: mean arterial pressure, PAP: pulmonary artery pressure, LAP: left atrial pressure, RAP: right atrial pressure. *$P < .01$; **$P < .05$

Table 2. Changes of hemodynamic parameters before and after ASD opened

Group	CO (L/min)	PAWP mmHg	SVRI (N·s·m-2·L-1)	PVRI* (N·s·m-2·L-1)	ELWI ml/kg
Opened ASD	3.1±1.3	11.8±2.1	270.1±113.6	33.4±7.2	16.6±6.2
Closed ASD	2.4±1.4	13.5±3.2	268.3±107.9	45.2±9.2	18.2±6.1
P-value	.1669	.0964	.9648	.0005	.4821

CO: cardiac output, PAWP: pulmonary artery wedge pressure, SVRI: Systemic Vascular Resistance Index, PVRI: Pulmonary Vascular Resistance Index, ELWI: Extravascular Lung Water Index. *P < 0.01.

Observation indexes when ASD closed and opened: After ASD was opened, CPB was continued to support the heart. Fifteen minutes later, the myocardial contraction gradually enhanced, the circulation became stable, heart function obviously improved, and CPB smoothly stopped. After that, the catheters of SVC, IVC and BA were preserved and started to work simulating VA-ECMO. Only ASD was opened or closed with other experimental conditions remaining unchanged. When ASD was closed, UCG showed that the atrial shunt disappeared (Figure 1). VA-ECMO was used with 40% oxygen concentration, while indexes showed PaO_2: 141.2±21.4 mmHg, PaO_2/FiO_2: 353.0±53.5, HR: 108±17 beats/min, MAP: 49.3±13.5 mmHg, the heart looked full, range of motion was small, and contraction weak. When ASD was opened, the left-to-right shunt was found (Figure 2). Additionally, PaO_2 increased to 169.3±18.9 mmHg, PaO_2/FiO_2: 423.3±47.3, HR: 98±18 beats/min, and MAP: 68.2±16.1mmHg, the range of cardiac motion obviously was increased, heart beat was relaxed, and the condition of systemic circulation obviously was improved. Statistical analysis showed that MAP, PAP, PVRI, PaO_2, SaO_2, PaO_2/FiO_2, DO_2 significantly were different between opened and closed ASD condition ($P < .01$). Indicators of change can be seen in detail (Tables 1, 2, 3, and 4).

DISCUSSION

LPS is the main component of the endotoxin of gram-negative bacteria. The animal model of ARDS can be made by intravenous or inhalation of LPS, which is one of the commonly used methods at present [Yuan 2018]. The model is very useful in the study of pathogenesis, pathophysiology, diagnosis and treatment of ARDS including COVID-19. The pathological changes of lung injury caused by COVID-19 are mainly pulmonary edema and alveolar edema after lung interstitial and alveolar injury. In severe cases, it can develop into hyaline membrane formation of alveoli, which leads to the pathological and clinical manifestations of ARDS [Xu 2020]. The patients suffered from refractory hypoxemia and respiratory distress, due to severe ventilation/blood flow imbalance, intrapulmonary shunt, and diffusion disorder. In order to alleviate hypoxemia, oxygen therapy is necessary, but it still is difficult to correct hypoxemia in critical patients. In this experiment, we successfully made the animal model of ARDS by the method of LPS intravenous pump and carried out the CPB experiment. Compared with the animal model induced by LPS inhalation, it can better simulate the pathological and pathophysiological changes of COVID-19, including lungs and systemic lesions [Zhang 1999].

For ARDS patients combined with LVD, VA-ECMO should be a choice. However, clinical data shows that the mortality rate of patients with VA-ECMO is very high in COVID-19 [Zhang 2020]. Although there is no detailed data reported in the literature, ARDS combined with LVD is one of the main causes of death in COVID-19. For these kinds of critical patients, VA-ECMO or VAV-ECMO is installed, but the result is not optimistic, multiple organ dysfunction syndrome (MODS) gradually occurs. We analyzed the reason under VA-ECMO working mode: The oxygenated venous blood could not reach the aortic root, so the blood supply to the heart and brain was still the hypoxic blood circulating from the lung [Kon 2017]. Therefore, the symptoms of patients could not be relieved or even worsened. In order to solve this problem, VAV-ECMO model can be applied, but it is difficult to control the flow to the artery and vein. It also cannot solve the problem of cardiac blood supply very well; meanwhile, its support to cardiopulmonary function is limited, so it rarely is used in clinic. Based on these reasons, we designed ASD plus VA-ECMO to treat ADRS combined LVD with the concept of "strengthening heart and compensating lung, cure heart and lung together." Just like the routine application of left heart drainage to improve left ventricular function after heart operation, the presence of ASD allows the left

Table 3. Changes of mechanical parameters of lung before and after ASD opened

Group	PIP (kPa)	P_m (kPa)	RAW (kPa·L^{-1}·s^{-1})	C_{dyn} (ml/kPa)
Opened ASD	1.99±0.26	0.69±0.28	2.47±0.73	141.9±41.8
Closed ASD	2.02±0.25	0.71±0.33	2.66±0.69	151.2±43.1
P-value	.7497	.6604	.7291	.8364

PIP: peak airway pressure, P_m: mean airway pressure, RAW: airway resistance, Cdyn: pulmonary dynamic compliance

Table 4. Changes of parameters of lung gas exchange and oxygen metabolism before and after ASD opened

Group	PaO_2* (mmHg)	$PaCO_2$ (mmHg)	SaO_2* (%)	PaO_2/FiO_2*	DO_2 (ml·min-1·m-2)	VO_2 (ml·min^{-1}·m^{-2})	O_{2ext} (%)
Opened ASD	169.3±18.9	38.2±4.2	98.2±1.1	423.3±47.3	411.2±166.8	47.1±30.1	13.1±4.6
Closed ASD	141.2±21.4	40.1±3.4	96.1±1.3	353.0±53.5	398.5±108.3	48.6±30.5	12.9±4.4
P-value	0.0007	0.1841	0.0001	0.0007	0.7864	0.9710	0.6987

PaO_2: arterial oxygen partial pressure, PaCO2: carbon dioxide partial pressure, SaO_2: oxygen saturation, PaO_2/FiO_2: Oxygenation Index, DO_2: Oxygen Transport, VO_2: Oxygen Consumption and O_{2ext}: Oxygen Uptake Rate. *$P < .01$

atrial blood shunt to the right atrium via ECMO and enter the aorta. At the same time, it significantly can reduce the left ventricular preload, ensure the left ventricle relax adequately, or even empty pump [Baruteau 2018]. The aortic valve is not open, and the blood oxygenated by ECMO also can reach the aortic root. At the same time, the pressure of the left atrium is decreased, pulmonary edema is reduced, pulmonary circulation is improved, and the oxygen supply of heart and brain is ensured. This improves the heart function and blood supply of organs and tissues in the whole body. The results of this experiment confirm that our analysis is correct.

Atrial septostomy is a routine technique in the department of cardiac intervention. It safely can be performed with the assistance of X-ray or UCG (intravascular /esophageal / conventional) [Lin 2017]. The size of 1-2cm ASD will not affect the later cardiac function of patients, and ASD smaller than 1cm is not sufficient for proper LV decompression [Geva 2014]. Therefore, in most cases, these patients do not need to perform atrial septal closure surgery after recovery [Dahdouh 2013]. If it is found in the later follow up that patients have excessive systemic pulmonary shunt, right heart overload and increased pulmonary artery pressure due to ASD, they also can choose to undergo percutaneous atrial septum defect closure [Yi 2019].

Limitations of this experiment: Although intravenous injection of LPS is the best way to simulate ARDS caused by severe infection at present, it still has difference with ARDS caused by COVID-19. In addition, the application of extracorporeal circulation in this experiment cannot completely be equivalent to ECMO, but the working principle of the two is the same. ECMO is developed on the basis of CPB. The main difference between them is that the former is open, and the latter is closed. The difference in this aspect mainly affects the long-term use effect, which will not affect the results of this acute animal experiment. There also are different ways of venous return. ECMO is active suction, while CPB is gravity drainage. Although the return ways are different, both are negative pressure suction to achieve the full effect of venous drainage and can be well controlled. As for the position of aortic cannulation, the method of inserting the main artery of the head and arm into the aortic perfusion tube was used in this experiment, and the effect was the same as that of the subclavian artery cannulation in ECMO. The difference between these two aspects is not significant. Therefore, the results of this experiment can be used as a reference for the treatment of ARDS with LVD caused by COVID-19, but it needs further clinical validation. We also will follow up iatrogenic ASD (1-1.5 cm) and its further impact on patient quality of life.

REFERENCES

Baruteau AE, Barnetche T, Morin L, et al. 2018. Percutaneous balloon atrial septostomy on top of venoarterial extracorporeal membrane oxygenation results in safe and effective left heart decompression. Eur Heart J Acute Cardiovasc Care 7:70-79.

Brann SH, Thomas CN, Rose SS, et al. 2000. The feasibility of a porcine model of acute coronary occlusion and reperfusion using off-pump coronary artery bypass grafting. West Indian Med J 49:271-275.

Dahdouh Z, Roule V, Lognone T, et al. 2013. Atrial septostomy in cardiogenic shock related to H1N1 infection. Acute Card Care 15:7-9.

Dahdouh Z, Roule V, Lognone T, Sabatier R, Grollier G. 2012. Percutaneous blade and balloon atrioseptostomy as a supplement to extracorporeal membrane oxygenation as a bridge to heart transplantation. Cardiovasc Revasc Med 13:69–71.

Franklin M, McGough E, Peng Y. 2019. Percutaneous mechanical devices for supporting the left ventricular failure. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 44(4):354–363.

Geva T, Martins JD, Wald RM. 2014. Atrial septal defects. Lancet. 383(9932):1921-1932.

Kon ZN, Bittle GJ, Pasrija C, et al. 2017. Venovenous Versus Venoarterial Extracorporeal Membrane Oxygenation for Adult Patients With Acute Respiratory Distress Syndrome Requiring Precannulation

Hemodynamic Support: A Review of the ELSO Registry. Ann Thorac Surg 104:645-649.

Lin YN, Chen YH, Wang HJ, et al. 2017. Atrial Septostomy for Left Atrial Decompression During Extracorporeal Membrane Oxygenation by Inoue Balloon Catheter. Circ J 81:1419-1423.

Meuwese CL, de Haan M, Zwetsloot PP, et al. 2020. The hemodynamic effect of different left ventricular unloading techniques during veno-arterial extracorporeal life support: a systematic review and meta-analysis. Perfusion 267659119897478.

Millar JE, Bartnikowski N, von Bahr V, et al. 2019. Extracorporeal membrane oxygenation (ECMO) and the acute respiratory distress syndrome (ARDS): a systematic review of pre-clinical models. Intensive Care Med Exp. 7(1):18. Published Mar 25.

Ramanathan K, Antognini D, Combes A, et al. 2020. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med.

Xu Z, Shi L, Wang Y, et al. 2020. PATHOLOGIC findings of COVID-19 associated with acute Respiratory distress syndrome, The Lancet Respiratory Medicine.

Yang X, Yu Y, Xu J. 2020. Clinical course and outcomes of critically patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, study, The Lancet Respiratory medicinal.

Yi K, Xu J, You T, Hou X, Ma L, Wang D, Yang K. 2019. Comparison of efficacy of percutaneous transcatheter closure of atrial septal defect by radiation-guided versus ultrasound-guided transcatheter closure: A Meta-analysis. Chinese Journal of Heart and Lung Disease, 3805:573-580.

Yuan Z, Bedi B. 2018. Bronchoalveolar Lavage Exosomes in ipopolysaccharide-induced Septic Lung Injury. J Vis Exp.

Zhang C, Huang S, Zheng F. 2020. Controversial treatments: an updated understanding of the Coronavirus Disease 2019. J Med Virol.

Zhang H, Chao Y, Ma S, et al. 1999. A sheep Acute respiratory distress syndrome model was established by intravenous injection of endotoxin under anesthesia. Critical Care Medicine in China 02:13-15.

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. Published online March 9.