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Selective Recruitment of Large Lower Lobe Atelectasis on Donor Back Table in Rejected Donor Lungs

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Background. Large atelectatic areas in donor lungs are frequently resistant to standard recruitment maneuvers, producing a tenaciously low PO_2/FiO_2 ratio. The aim of this study is to investigate the optimal protocol for the recruitment of large atelectatic areas in the context of ex vivo lung perfusion (EVLP). **Methods.** Seventeen rejected lungs with large lower lobe atelectasis (≥40%) were divided into 2 groups: manual resuscitation (n = 5) and selective recruitment (n = 12). Transplant suitability was then evaluated in cellular EVLP. In the manual resuscitation group, following bronchoscopy, if the conventional recruitment maneuver was not successful, a bagging technique was utilized to resolve atelectasis in EVLP. In the selective recruitment group, a pediatric endotracheal tube was introduced to the lower lobe bronchus on the back table of the donor hospital. Selective recruitment of the lower lobe was accomplished while keeping peak inspiratory pressure <30 cm H_2O for 30 seconds. **Results.** The average atelectasis size and lung weight in 17 donor lungs was 75.4 ± 20.6% and 960 ± 221 g, respectively. There were no significant differences between the 2 groups in all donor variables, except cold ischemic time (P = 0.001, 5.2 ± 0.5 versus 6.4 ± 0.7 hours). The selective recruitment group was associated with better transplant suitability (P = 0.035, 75% versus 20%), better PO_2/FiO_2 ratio (P = 0.186, 324 ± 89 versus 258 ± 87 mm Hg), lower lung weight (P = 0.057, 997.9 ± 229.2 versus 1377.2 ± 452.9 g), and better pathological score (P < 0.05, 1.0 ± 1.3 versus 2.8 ± 0.8) than the manual resuscitation group. **Conclusion.** A selective recruitment procedure is a safe and effective method of eliminating large atelectasis before EVLP.

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Atelectasis occurs in approximately 90% of anesthetized patients.[1] Atelectasis may contribute to hypoxemia, especially when there are risk factors of atelectasis, such as mechanical ventilation, supine position, and obesity.[2,3] The effects of atelectasis include decreased pulmonary compliance, increased shunt, increased pulmonary vascular resistance, and lung injury.[4] Similarly, atelectasis may be the main contributor to low oxygenation in the donor lung necessitating the use of strategic ventilation, using recruitment maneuvers, in the management of the donor lung.[5,6] Routine use of bronchoscopy and regular airway suction might be beneficial.[7] Hanna and colleagues[8] reported that airway pressure release ventilation improved PO_2/FiO_2 (P/F) ratio and increased the donor lung utilization rate (84% versus 18%) when compared with assist/control ventilation. The graft survival of both groups was better than the national average. It is suspected that the resolution of atelectasis might contribute to better oxygenation in the airway pressure release ventilation group.[8]

Ex vivo lung perfusion (EVLP) is utilized in the management of marginal donor lungs. One mechanism of improving lung function is to eliminate atelectasis with a recruitment maneuver. We sometimes, however, encounter a case where a standard recruitment maneuver utilizing either high positive end-expiratory pressure (PEEP) or high tidal volume does not eliminate large lower lobe atelectasis. During the mechanical breath, the majority of inspiratory flow is delivered to the upper and middle lobes, whose pulmonary compliance is significantly higher than that of atelectatic lower lobes,[9-11] as shown in Figure 1. Relatively higher pressure is required at the airway opening in the atelectatic area with the additional concern of decreased cardiac output and endangering the entire lung field to excessive pressure/volume and would selectively risk the areas of highest compliance. We hypothesized that a selective recruitment procedure in donor back table might protect pulmonary lung function of rejected donor lungs with large lower lobe atelectasis. The aim of this study is to investigate the optimal protocol for the recruitment of large atelectatic areas in the rejected donor lungs in the context of EVLP.

MATERIALS AND METHODS

Study Design

Seventeen rejected donor lungs with large lower lobe atelectasis were obtained for research EVLP from a local organ procurement organization and divided into 2 groups: the manual resuscitation group (n = 5) and the selective recruitment group (n = 12). We first tested 5 lungs in each group and noted profound damage in the manual resuscitation group. Thereafter, we tested 7 more in the selective recruitment group to be sure to have no positive donor selection bias. In the manual resuscitation group, following bronchoscopy, if the conventional recruitment maneuver was not successful, a bagging technique was utilized to resolve atelectasis in EVLP (Figure 2). In the selective recruitment group, selective lower lobe recruitment was performed on the back table in the donor hospital as described below, followed by cold preservation and EVLP. This study was approved by the Cleveland Clinic Institutional

Review Board (No. 11–737). The humans involved in this study were treated in a manner in accordance with the Declaration of Helsinki and the Declaration of Istanbul.

Donor Selection Criteria

Research donor lungs were obtained from local organ procurement organization (Lifebanc) as follows: (1) donor lungs were declined by a clinical team; (2) the average atelectasis size at the inspection of the chest was ≥40%; and (3) lung weight on donor back table was <1300 g. Donation after circulatory death lungs were included. Donors had no premorbid history of lung disease. Severe pulmonary infection, bilateral lung contusion, severe bullous emphysema, and severe bilateral aspiration were excluded in the study.

Lung Procurement

The procurement procedure was basically performed according to our clinical protocol. The 1 difference was that the lung recruitment maneuver with high peak inspiratory pressure (25–30 cm H_2O for 30 s) in the chest was not performed, as detailed in the limitations that follow. Briefly, 4 L of Perfadex was flushed through the pulmonary artery. Following explanting lung blocks, a selective recruitment was performed on the back table in the selective recruitment group. Retrograde flush was done with 2 L of Perfadex, and cold preservation was initiated.

Atelectatic Area in Donor Lungs

Atelectatic size during procurement was recorded by our research lung procurement team. Atelectatic size was defined as the percentage of atelectatic area on the diaphragmatic surface of the lower lobe. The atelectatic size was expressed as an average of atelectatic area in both lower lobes.

Donor Hospital Back Table Selective Recruitment Procedure

A pediatric endotracheal tube (5.5 mm ID) was introduced to the lower lobe bronchus and the balloon cuff inflated. The tracheal tube was connected to a manual resuscitator bag with a manometer. Selective recruitment of the lower lobe
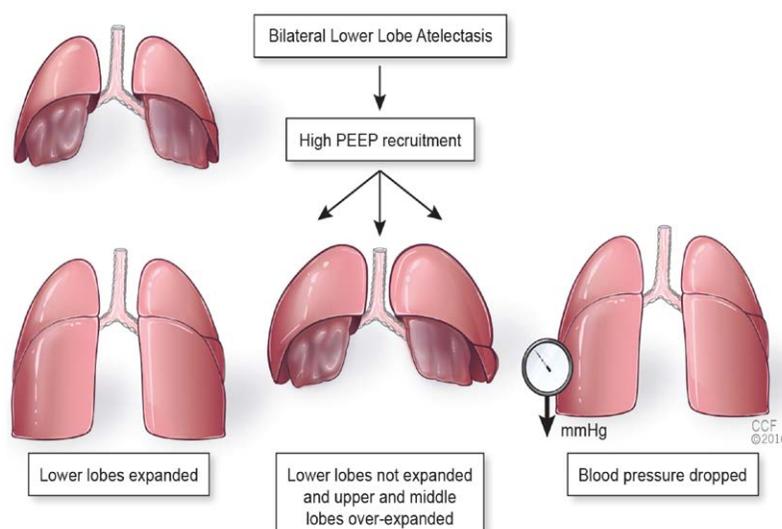

FIGURE 1. Three possible outcomes of high PEEP recruitment in bilateral total lower lobe atelectasis through the trachea. (1) Lower lobes are fully expanded. (2) Upper and middle lobes are overexpanded, whereas lower lobes are not expanded. (3) Blood pressure drops. EVLP, ex vivo lung perfusion; PEEP, positive end-expiratory pressure.
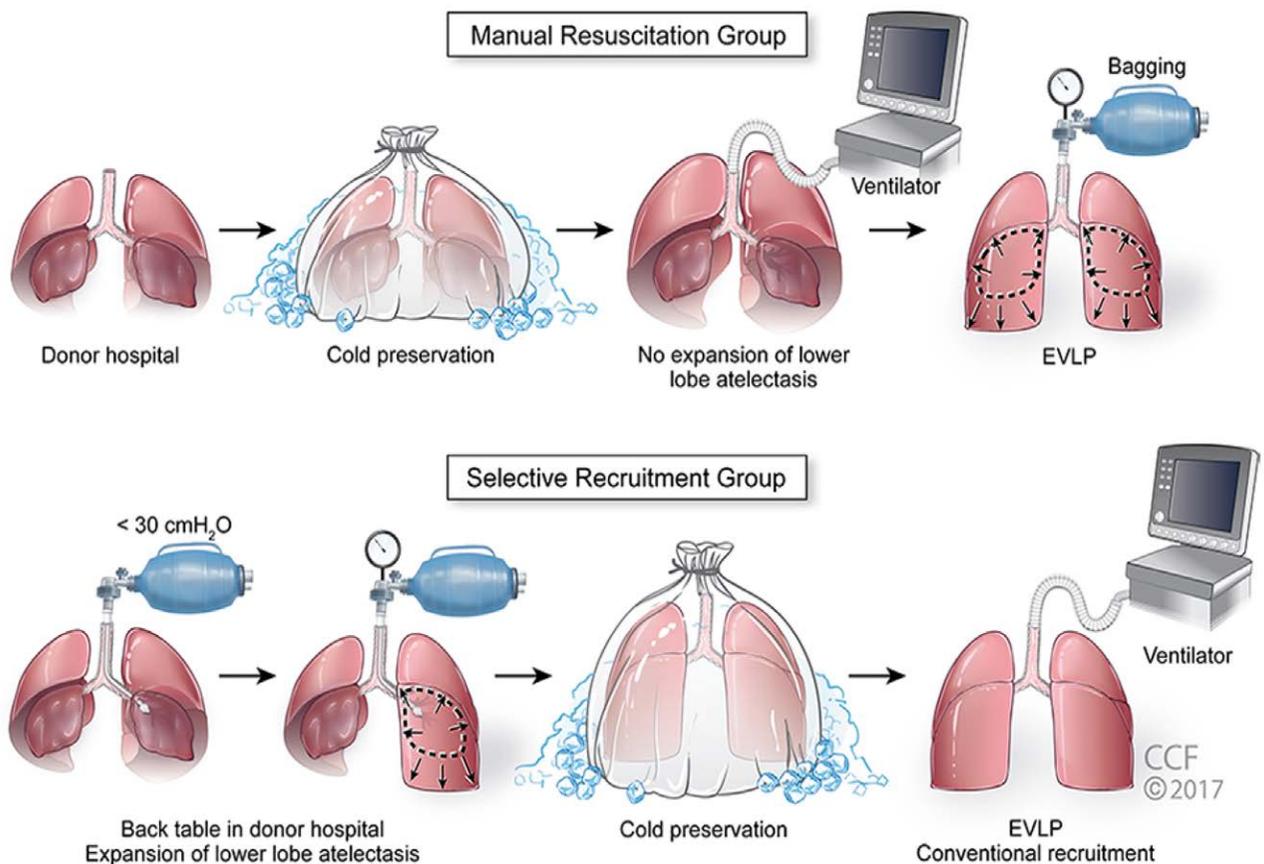
FIGURE 2. Study layout. In the manual resuscitation group (n = 5), donor lungs with large atelectasis were preserved in cold lung preservation solution. Following no success of opening atelectasis by conventional recruitment maneuvers (high PEEP and high tidal volume) in EVLP, atelectatic lesions were opened by using bagging procedure. In the selective recruitment group (n = 12), following lung procurement, atelectasis was completely eliminated by selective recruitment procedure in the back table of the donor hospital as shown in Figure 3. Then, lungs were stored in cold lung preservation solution. Transplant suitability was evaluated according to physiological parameters at 2 h of EVLP. EVLP, ex vivo lung perfusion; PEEP, positive end-expiratory pressure.

was accomplished while keeping peak inspiratory pressure of 25–30 cm H_2O for 30 seconds (Figure 3). The procedure was performed at both sides. Following the recruitment maneuver, the trachea was clamped, and then cold preservation was initiated following retrograde flush.

Cellular EVLP

Vivoline LS1 (Vivoline Medical AB, Lund, Sweden) was utilized with cellular perfusate, 100% of estimated cardiac output, and an open left atrium, as previously reported.[12] Briefly, the lungs were gradually warmed to a target of 37°C. At 37°C, tidal volume was increased to 6 mL/ideal body weight. The following 2 standard lung recruitment procedures were performed in both groups: (1) peak inspiratory pressure of 25–30 cm H_2O for 30 seconds and (2) tidal volume 10 mL/kg, PEEP 5 cm H_2O, respiratory rate 10/min, and 10 minutes. Using physiological parameters at 2 hours, transplant suitability was evaluated, according to the Lund protocol.[13,14]

Manual Resuscitation Procedure

During EVLP, manual resuscitation procedure was initiated when large lower lobe atelectasis was not resolved by 2 standard lung recruitment procedures. The airway was connected to a resuscitation bag, and manual bagging procedure (5–10 ventilations/15 s) was performed until atelectasis was eliminated.

Lung Tissue Analyses

Lung tissue was taken from the middle lobe and the left lower lobe at the end of EVLP. Formalin-fixed lung tissue was sectioned at 5 μm, and hematoxylin and eosin–stained slides were reviewed. Pathological scoring was performed by a pulmonary pathologist (C.F.) in a blind fashion: 0, absent; 1, focal; 2, diffuse; in acute lung injury, acute inflammation, and hemosiderin deposition.

Statistical Analysis

All data were expressed as a mean ± standard deviation. Parametric data were compared by Student's *t*-test. The categorical parameters in donor demographics, pathological score, and transplant suitability were analyzed by Fisher exact test, Mann-Whitney test, and Pearson Chi-square test, respectively. All statistical analyses were performed using JMP Version13.1.0 (SAS Institute Inc, NC). This study considered probability values of $P < 0.050$ as significant.

RESULTS

Donor Demographics of Perfused Lungs

Average donor age was 45.0 years, including 8 women and 9 men. Twelve donors were smokers, with an average of 16.7 pack-years. Body mass index (BMI) was 35.0 ± 11.4 kg/m². The average final P/F ratio was 216.5 mm Hg. Atelectatic
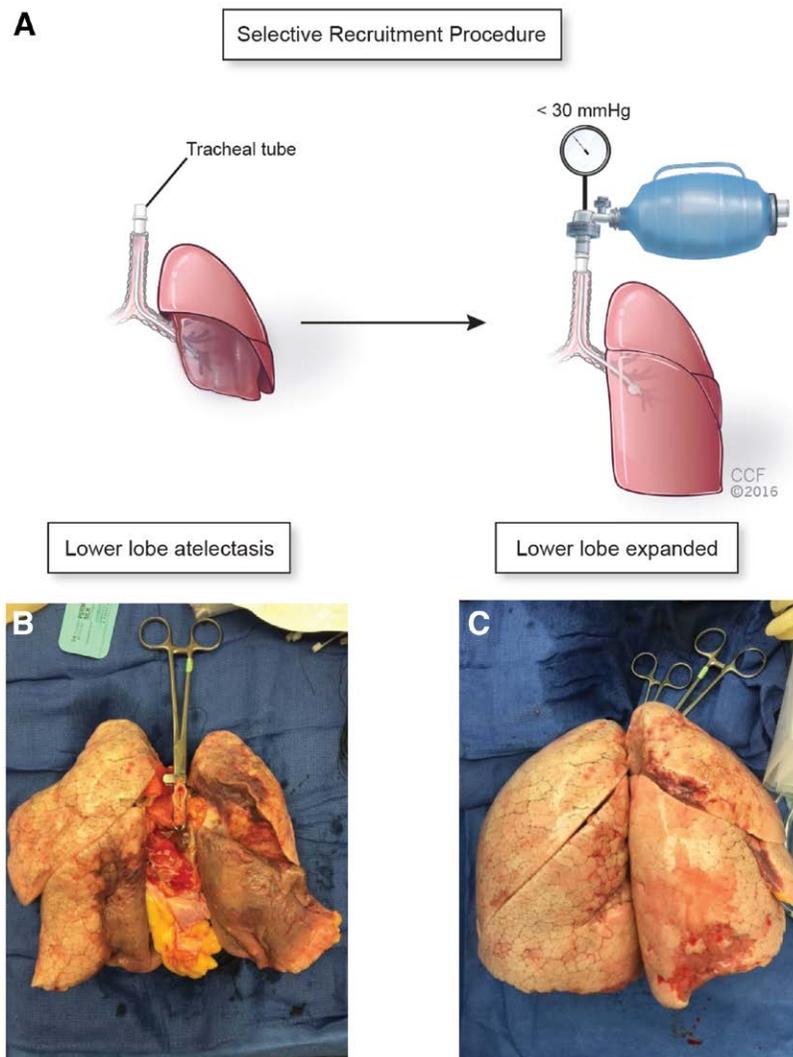
FIGURE 3. Selective recruitment procedure of large lower lobe atelectasis on the back table. A, Selective recruitment procedure in back table of the donor hospital. Pediatric tracheal tube (5.5 mm ID) was introduced to the lower lobe bronchus, and balloon cuff was inflated. The tracheal tube was connected to Ambu bag with a manometer. Selective recruitment of the lower lobe was done with the maximum airway pressure <30 cm H_2O for 30 s. Then, the trachea was clamped at approximately 50% of total lung capacity. B, The backside view of rejected donor lung with large lower lobe atelectasis in the back table of the donor hospital. Atelectasis size was 80% in the left lower lobe and 100% in right lower lobe. C, In the selective recruitment procedure, both sides of atelectasis were completely opened up using the pressure of <30 cm H_2O in the lower lobe bronchus.

area was 75.4%. The mean cold ischemic time was 5.5 hours (Table 1). There were no significant differences between the selective recruitment and the manual resuscitation groups in all variables, except cold ischemic time (Table 1).

EVLP of 2 Groups

In all cases of the manual resuscitation group (n = 5), the conventional recruitment maneuver was not successful, and then the bagging technique was utilized to re-expand atelectasis in EVLP. In 80% (4/5) of cases, lungs were not suitable for transplant (Table 1). In the selective recruitment group (n = 12), selective re-expansion of lower lobe atelectasis was performed on the back table of the donor hospital, and the atelectatic area was successfully eliminated in all cases. In EVLP, lower lobes were fully re-expanded. Seventy-five percent (9/12) of perfused lungs were judged as suitable for transplant. There was a statistically significant difference in transplant suitability between the 2 groups (P < 0.050). The selective recruitment group had a higher P/F ratio, lower lung weight, and lower

cases of positive airway fluid than the manual resuscitation group without significant differences (Table 1).

Pathological Evaluation of Lung Tissue

Pathological score was significantly lower in the selective recruitment group than in the manual resuscitation group (P = 0.033, 1.0 ± 1.3 versus 2.8 ± 0.8, Figure 4A). The representative pathological findings of the 2 groups are demonstrated in Figure 4B and C. The finding of the selective recruitment group was predominantly unremarkable alveolated lung parenchymal with focal mild congestion (right upper). The pathological finding of the manual resuscitation group was diffusely congested alveolated lung parenchyma with reactive pneumocytes and early acute lung injury.

DISCUSSION

Sanchez and colleagues[15] have reported that the elimination of atelectasis is 1 mechanism of organ repair in EVLP.

Selective recruitment group vs manual recruitment group

Groups	Selective recruitment	Manual resuscitation	P
No.	12	5	
Donor demographics			
Age	48.1 ± 12.0	42.2 ± 14.6	0.394
Male	6, 50%	3, 60%	0.707
BMI, kg/m^2	34.6 ± 11.7	35.9 ± 11.9	0.843
DCD	4, 30%	1, 20%	0.582
Cause of death			
Anoxia	6, 50%	5, 100%	0.277
Cerebrovascular/stroke	1, 8%	0	
Head trauma	3, 25%	0	
Others	2, 16%	0	
Final P/F ratio, mm Hg	216.5 ± 66.6	216.6 ± 90.0	0.998
Abnormal CXR	12, 100%	5, 100%	NA
Smoking history	8, 66%	4, 66%	0.582
Smoking, pack-year	16.8 ± 5.1	16.4 ± 7.9	0.964
Ventilation, days	5.5 ± 3.9	4.9 ± 1.2	0.754
CIT, h	5.2 ± 0.5	6.4 ± 0.7	**0.001**
Atelectasis size, %	72.5 ± 19.3	82.5 ± 24.3	0.381
Lung weight, g	910.4 ± 217.7	1082.2 ± 199.6	0.150
Transplant suitability			
Suitable	9, 75%	1, 20%	
Nonsuitable	3, 25%	4, 80%	**0.035**
EVLP parameters			
P/F ratio, mm Hg	324.3 ± 89.8	258.6 ± 87.4	0.186
Peak airway pressure, cm H$_2$O	11.5 ± 1.3	11.8 ± 2.2	0.740
Plateau pressure, cm H$_2$O	8.5 ± 0.9	8.4 ± 1.3	0.744
PVR, dyn·s/cm^5	332.6 ± 87.0	319.7 ± 30.0	0.754
Lung weight, g	997.9 ± 299.2	1377.2 ± 452.9	0.057
Lung weight change, g	87.5 ± 215.3	295 ± 423.7	0.193

Atelectasis size was calculated as mean of atelectasis percentage of bilateral lower lobes. Lung weight change, lung weight change during ex vivo lung perfusion. Data are expressed as mean ± standard deviation. Bold values indicate abnormal value.
BMI, body mass index; CIT, cold ischemia time; CXR, chest x-ray; DCD, donation after circulatory death; EVLP, ex vivo lung perfusion; NA, not available; P/F, PaO$_2$/FiO$_2$; PVR, pulmonary vascular resistance.

Obviously, it is not difficult to eliminate small atelectatic areas by using recruitment maneuvers. Yet, it has been unknown if larger atelectatic areas could be eliminated in EVLP. Rothen et al[16] reported that lobar atelectasis was eliminated by a recruitment maneuver using a maximum airway pressure of 40 cm H$_2$O during general anesthesia. Tusman and colleagues[17] emphasized the importance of high initial pressure of 40 cm H$_2$O to overcome the alveolar collapse. In the Toronto lung transplant program, a maximum of 15–20 cm H$_2$O is applied to recruit donor lung atelectatic areas.[18] However, the success rate of lung recruitment of large atelectatic areas with 15–20 cm H$_2$O of PEEP remains unknown.

The initial significant finding of this study was that all of the large atelectatic area lungs (5/5) in the manual resuscitation group were unresolved by the standard recruitment maneuver using high PEEP (30 cm H$_2$O) and high tidal volume (10 mL/ideal body weight) in EVLP. This result might be ascribed to the fact that there is no "chest wall" in EVLP to stabilize and constrain upper/middle lungs. Using the clamp/balloon occlusion technique of upper/middle lobe bronchus and insufflation might be considered to selectively ventilate atelectatic lower lobe.[9,10] However, clamping the upper/middle lobe bronchus results in bronchial injury and ballooning

through bronchoscopy might be challenging due to this intricacy. Manual resuscitating (bagging) was originally documented by Clement et al,[19] who proposed that bagging is effective to clear secretions and reinflate atelectatic areas. Barotrauma was, however, suspected with peak airway pressures as high as 91–56 cm H$_2$O during bagging.[20] Björklund et al[21] reported that bagging with a few large breaths at birth compromises the effect of surfactant replacement in lambs.

In the manual resuscitation group, atelectasis was eliminated by the bagging procedure in EVLP. The manual resuscitation group demonstrated significantly lower transplant suitability, poorer lung function, and a poorer pathological score than the selective recruitment group. The results might be explained by several mechanisms. First, increased airway pressure/volume during the bagging procedure might cause barotrauma/volutrauma.[20,21] Second, the collapse of alveolar space during cold preservation might be related. Previous studies have described that oxygen is necessary during cold storage to maintain aerobic metabolism.[22,23] Fukuse et al[24] demonstrated that a deflated lung status during cold storage is associated with poorer pulmonary function than other groups in an ex vivo rat lung model. Moreover, it was reported that atelectasis led to a significant maldistribution of lung preservation solution with an increased water content.[25] Therefore, it might suggest that the cold storage of a largely collapsed lobe had a negative impact, although Bansal et al[26] reported 1 successful lung transplantation of a donor lung with persistent lobar atelectasis. Third, re-expansion pulmonary edema might be related. Re-expansion pulmonary edema has been reported when collapsed lung is re-expanded in a short period of time. Evidence has demonstrated that the major etiology of re-expansion edema is increased pulmonary vascular permeability, which might be caused by hypoxic injury, increased pulmonary vascular pressure and blood flow, decreased surfactant, and mechanical damage.[27] The study of porcine warm ischemia lung model by Lindstedt et al[28] might be related. They demonstrated that the ventilation using increased PEEP of 10 cm H$_2$O for 10 minutes without perfusion during EVLP was associated with better oxygenation, lower airway pressure and lower lung weight in cellular EVLP system. It is suggested that the ventilation with no flow may contribute to improved pulmonary function because of reduced mechanical stress in endothelial cells.

DeCampos and colleagues[29] reported that inflation to total lung capacity for 10-minute ventilation before reperfusion reduced mechanical stress-induced injury in an ex vivo rat lung model. However, it was impossible to expand large atelectatic areas in a nonselective fashion during EVLP as shown in the manual resuscitation group. Moreover, any procedure of ventilation following cold storage might induce mechanical stress, based on the relatively low compliance of lungs at low temperature.[30] Along with the previous data supporting the inflated lung during cold storage,[22-24] we tried the re-expansion of large atelectatic areas before cold preservation. Hansen et al[11] reported that selective recruitment maneuvers effectively eliminated lobar atelectasis without affecting other lobes in a porcine model. Insufflation to the pressure of 40 cm H$_2$O for 30 seconds was performed using the inner lumen of the bronchial blocker. In the present study, a selective recruitment was applied to large lower lobe atelectatic area on the back table of the donor hospital (Figure 2), and this maneuver successfully recruited collapsed lungs. Moreover, the selective
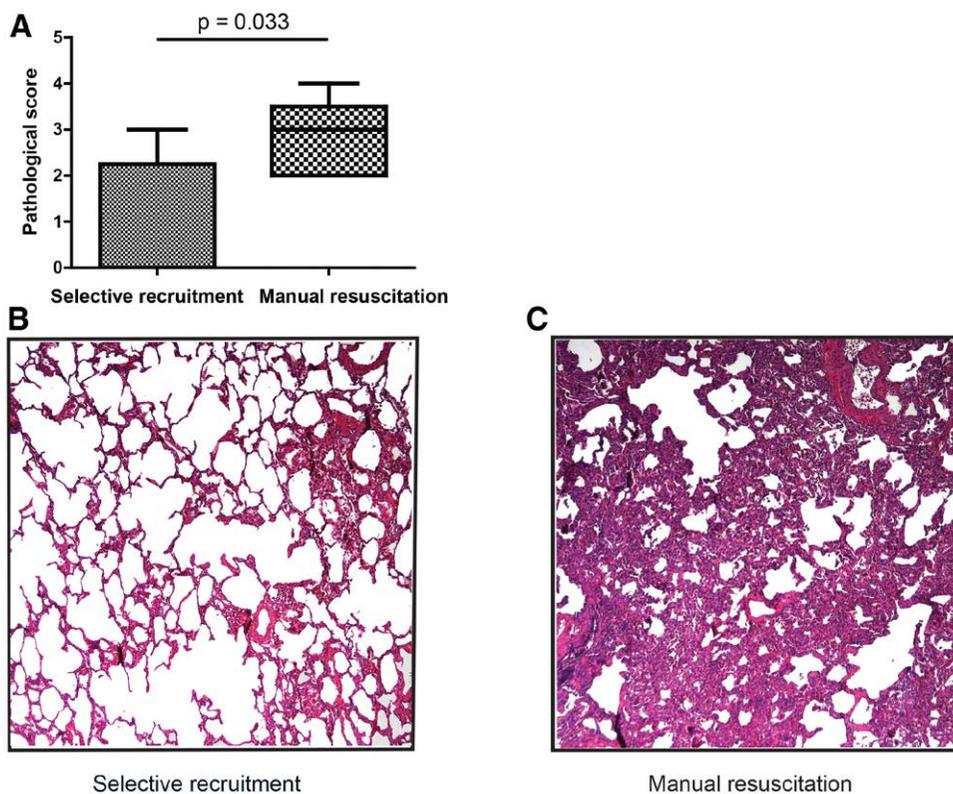
FIGURE 4. Pathological evaluation of lung tissue. A, Pathological score was significantly lower in the selective recruitment group than in the manual resuscitation group (1.0 ± 1.3 vs 2.8 ± 0.8, *P* = 0.033). B, Typical finding of the selective recruitment group (hematoxylin and eosin; ×40): predominantly unremarkable alveolated lung parenchymal with focal mild congestion (right upper). C, Typical finding of the manual resuscitation group (hematoxylin and eosin; ×40): diffusely congested alveolated lung parenchyma with reactive pneumocytes and early acute lung injury.

recruitment group was associated with significantly better transplant suitability, higher oxygenation, lower lung weight, and a better pathological score than the manual resuscitation group. These data indicate that selective expansion of large atelectatic areas before cold storage might be a safe and effective method to rescue rejected donor lungs with atelectasis and a poor P/F ratio.

In the previous study of 84 cases of nontransplanted donor lungs, which demonstrated the correlation between chest x-ray scoring and lung weight, the radiographic findings of atelectasis were positive in 45% of cases in the right side and in 64% in the left side.[31] It is suggested that atelectasis might be present in a significant portion of rejected donor lungs, resulting in poor oxygenation and lower lung utilization. In the analysis of direct inspection in both standard and rejected donor lungs during procurement, our group recently demonstrated that rejected lungs have a larger total atelectatic area than that of standard lungs.[32] Moreover, we find that the final P/F ratio in lung donors was significantly associated with either atelectatic area or BMI. In other words, donors with elevated BMI might have greater atelectatic areas, resulting in lower P/F ratio, compared with donors of normal BMI. This finding is consistent with the previous reports that morbid obesity was correlated to a higher frequency and larger atelectatic area in the dependent area during general anesthesia.[3] In the analysis of morbid obese patients (n = 20, mean BMI 46.5) and nonobese patients (n = 10), atelectasis was positive in 9.7% in morbid obese patients and 1.9% in control 24 hours after extubation. Obese patients have altered respiratory mechanics, including decreased chest wall and lung compliance and decreased functional residual capacity, in addition

to higher intra-abdominal pressure.[4] All of these factors result in decreased oxygenation during anesthesia, and it is easily expected that obesity causes poor oxygenation through the mechanism of atelectasis during organ donor management. The association between P/F ratio and either atelectasis or BMI might be useful in identifying the specific population of currently rejected lung donors with large areas of atelectasis. This donor population is important from the viewpoint of increasing the donor lung pool, because donor lungs with atelectasis might be re-expanded by lung recruitment and utilized in clinical lung transplant.

This study has several limitations. The case number was small, and thus there might represent a type II statistical error. Second, we had no high PEEP lung recruitment in the procurement. This was because the clinical procurement team did not allow us to perform this procedure because of the concern of unstable cardiovascular status. When the clinical use of lungs with a large atelectatic area is considered, a lung recruitment procedure will be applied, and the lung may be successfully re-expanded. Even if lung recruitment is not successful in the chest, selective recruitment procedure in the back table, and subsequent EVLP will salvage initially declined donor lungs at high rate. Third, the 2 study groups are not comparable, because the first illumination of atelectasis was performed before cold storage in the selective recruitment group and after cold storage in the manual resuscitation group. As discussed as the second reason why the manual resuscitation group was associated with poorer pulmonary function, the deteriorated lung function might be caused by delay in recruitment, not by bagging technique itself. Fourth, there was a statistically significant difference in cold ischemic time between the 2 groups

(5.2 versus 6.4 h). However, the cold ischemic time of both groups was within the acceptable cold ischemic time of lungs (<8 h), and the impact of the difference on the result of EVLP might be limited. Fifth, selective recruitment method was not performed during EVLP. This is because we expected that the procedure of selective recruitment method on EVLP might result in poor pulmonary function when lungs with large atelectasis were not recruited before EVLP. As already discussed,[22-24] a deflated lung status during cold storage is associated with poorer pulmonary function. Especially, significant large size (average: 75.4 ± 20.6%) of atelectasis in this study might have a severely negative impact on lung function on EVLP. However, this selective recruitment method is applicable on EVLP, when small size of atelectasis is resistant to the current standard recruitment method (high peak inspiratory pressure and manual compression of the upper lobe and the contralateral lobes) on EVLP.

In conclusion, all large lower lobe atelectatic areas were not re-expanded by a standard recruit maneuver in EVLP. Subsequent bagging procedure eliminated atelectasis but resulted in poor pulmonary function in EVLP, indicating that it might be difficult to properly eliminate large lower lobe atelectasis in EVLP. Conversely, selective recruitment technique in the donor hospital eliminated large lower lobe atelectasis, and the perfused lungs demonstrated better physiological parameters and transplant suitability in EVLP than the manual resuscitation group. This result indicates that the selective recruitment of the lower lobe is safe and applicable for the case of a large lower lobe atelectasis in the donor hospital before EVLP.

ACKNOWLEDGMENTS

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