Objectives: Acute respiratory distress syndrome is characterized by diffuse alveolar damage and increased extravascular lung water levels. However, there is no threshold extravascular lung water level that can indicate diffuse alveolar damage in lungs. We aimed to determine the threshold extravascular lung water level that discriminates between normal lungs and lungs affected with diffuse alveolar damage.

Design: A retrospective analysis of normal lungs and lungs affected with diffuse alveolar damage was performed.

Setting: Normal lung cases were taken from published data. Lung cases with diffuse alveolar damage were taken from a nationwide autopsy database. All cases of autopsy followed hospital deaths in Japan from more than 800 hospitals between 2004 and 2009; complete autopsies with histopathologic examinations were performed by board-certified pathologists authorized by the Japanese Society of Pathology.

Patients: Normal lungs: 534; lungs with diffuse alveolar damage: 1,688.

Interventions: We compared the postmortem weights of both lungs between the two groups. These lung weights were converted to extravascular lung water values using a validated equation. Finally, the extravascular lung water value that indicated diffuse alveolar damage was estimated using receiver operating characteristic analysis.

Measurements and Main Results: The extravascular lung water values of the lungs showing diffuse alveolar damage were approximately two-fold higher than those of normal lungs (normal group, 7.3 ± 2.8 mL/kg vs diffuse alveolar damage group 13.7 ± 4.5 mL/kg; \( p < 0.001 \)). An extravascular lung water level of 9.8 mL/kg allowed the diagnosis of diffuse alveolar damage to be established with a sensitivity of 81.3% and a specificity of 81.2% (area under the curve, 0.90; 95% CI, 0.88–0.91). An extravascular lung water level of 14.6 mL/kg represented a 99% positive predictive value.

Conclusions: This study may provide the first validated quantitative bedside diagnostic tool for diffuse alveolar damage. Extravascular lung water may allow the detection of diffuse alveolar damage and may support the clinical diagnosis of acute respiratory distress syndrome. The best extravascular lung water cut-off value to discriminate between normal lungs and lungs with diffuse alveolar damage is around 10 mL/kg. (Crit Care Med 2013; 41:00–00)

Key Words: acute lung injury; acute respiratory distress syndrome; autopsy; pulmonary edema; reference range; thermodilution

Acute respiratory distress syndrome (ARDS) is a rapidly progressive form of respiratory failure characterized by life-threatening hypoxemia and nonhydrostatic (permeability) pulmonary edema (1–3). Despite substantial progress in the understanding of the pathophysiology of ARDS, mortality rates remain high and lead to significant patient morbidity and healthcare burden (4, 5). The typical pathological feature of ARDS is diffuse alveolar damage (DAD), which...
may result in interstitial and alveolar edema and accumulation of extravascular lung water (EVLW (6–8)).

The American-European Consensus Conference (AECC) definition of acute lung injury (ALI)/ARDS was published in 1994 (1). Although the AECC criteria are simple and widely used, significant criticisms of these criteria have been reported (9–12). The studies of pathologic-clinical correlation have shown only modest agreement between the pathologic findings of DAD and the AECC diagnostic criteria (13–16). Although the Berlin definition for ARDS, recently published in 2012, has been shown to have better predictive validity for mortality than the AECC definition (17), there is still no pathologic-clinical validation (18). Therefore, diagnosis of DAD and evaluation of EVLW is still challenging in clinical settings (3, 10, 19).

The introduction of the transpulmonary thermodilution technique has allowed bedside evaluation of EVLW (20). The validation, accuracy (21–23) and precision (24, 25), of this technique has facilitated its adoption in the assessment of critically ill patients (26, 27). Although EVLW measurement was considered for inclusion in the Berlin definition, it was not included in the criteria because of the lack of sufficient evidence (17, 28). The normal EVLW value was previously shown to be approximately 7 ± 3 mL/kg (23). A recent meta-analysis suggests that normal values are unlikely to be found in critically ill patients (29). However, in the absence of threshold EVLW values indicating significant lung injury, EVLW has not been quantitatively verified.

Therefore, the aim of this study was to determine the threshold value of EVLW that discriminates between normal lungs and lungs affected with DAD using a nationwide autopsy database.

MATERIALS AND METHODS

This study compared the weights of both lungs from two data sources: normal lungs from previously published data (30) and lungs with DAD from a nationwide autopsy database (31). Institutional Review Boards of Nippon Medical School waived the need for approval for this retrospective study. In general, the weight of both lungs was measured before formalin fixation during autopsy. DAD is histologically diagnosed by the formation of hyaline membrane without taking lung weight into consideration (6).

Normal Lung Cases

We used data from a previous autopsy study that reported standard organ weights using data from consecutive 1,615 Japanese autopsy cases between January 1995 and November 2003, performed at the Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan (30). All autopsies were performed by pathologists authorized by the Japanese Society of Pathology (i.e., board-certified pathologists), and lungs were confirmed to be “normal” by morphologic evaluation and histologic diagnosis. Patients with abnormal lungs, such as those with pneumonia, DAD, or aspergillosis, and patients with malignant tumors identified during autopsy or by histological examination were excluded. The details of these concepts have been previously discussed (23, 30).

Lung Cases with DAD

To collect cases showing DAD, we used recent data over 6 years (2004–2009) from the “Annual of Pathological Autopsy Cases of Japan (31).” Data are recorded for all cases of autopsy after hospital deaths in Japan that include data from more than 800 hospitals and approximately 20,000 cases per year. This report was based on complete autopsies, with histologic examinations performed by board-certified pathologists. Patient age and sex, the hospital where the autopsy was performed, main clinical diagnosis (disease name), main pathologic lesions, and additional pathologic lesions (where histologic findings and lung weight were documented) are recorded every year. No detailed clinical information, such as clinical course of the patients or laboratory or radiographic data, was available. In order to avoid selection bias, we selected the cases on the basis of pathological diagnosis without considering the main clinical diagnosis. We carefully excluded the cases of patients with lung carcinoma, younger than 20 years old, and unrecorded lung weight. DAD was classified into direct or indirect lung injury according to the Berlin definition (17, 28).

Calculation of EVLW

On the basis of three previous studies (22, 23, 32), we calculated EVLW from lung weight. In accordance with our previous study (23), we used the equation for the correlation between clinical premortem EVLW and postmortem lung weight to estimate EVLW values from lung weight; EVLW (mL) = \([0.56 \times \text{lung weight (g)}) – 58\) (Fig. 1). An EVLW was indexed by predictive body weight (33–36). Further details are provided in the supplemental data (Supplemental Digital Content 1, http://links.lww.com/CCM/A654).

Statistical Analysis

Data were presented as mean values ± SD. Two groups were compared using two-sample t tests or the Mann-Whitney U test, as appropriate. For multiple-group comparisons, analysis of variance and the Kruskal-Wallis test were used. Receiver operating characteristic (ROC) curves were generated for the EVLW to discriminate the threshold between normal lungs and lungs with DAD. The area under the ROC curve, sensitivity, and specificity for discriminating the threshold of EVLW were evaluated. A positive predictive value of 99% for EVLW to detect DAD was estimated. The relationships between EVLW and age were assessed by coefficient of determination \(R^2\). A p value of less than 0.05 was considered significant. Statistical analyses were performed using SPSS 17.0 for Windows (SPSS, Chicago, IL).

RESULTS

Patients

There were 534 normal lungs (men, 223; women, 311) out of 1,615 examined during autopsy (30); detailed characteristics of the normal group are described elsewhere (23, 30). For the
DAD, 104,324 autopsies were performed and reported throughout Japan between 2004 and 2009; 1,688 cases (men, 1,169; women, 517) matched our entry criteria for DAD (Fig. 2). The average age was 69.0 ± 13.2 years (men, 68.9 ± 13.0; women, 69.3 ± 14.1). Among cases with DAD, 261 were reported as ARDS in the main clinical diagnosis of the annual.

Lung Weight
Lung weight was significantly higher, approximately two-fold, in the DAD group than in the normal group in both sexes (men, 873 ± 316 g vs 1,600 ± 495 g; p < 0.001; women, 641 ± 226 g vs 1,208 ± 402 g; p < 0.001) (Fig. 3). Lung weight of the men was significantly heavier than that of the women for both normal lungs (men, 873 ± 316 g; women, 641 ± 226 g; p < 0.001) and lungs with DAD (men, 1,600 ± 495 g; women, 1,208 ± 402 g; p < 0.001).

Estimated EVLW Value
After calculation of EVLW from the lung weight and indexing by predictive body weight, no significant differences in EVLW were found between the sexes in both normal and DAD groups (normal group: men, 7.4 ± 2.9 mL/kg vs women, 7.4 ± 3.1 mL/kg; p = 0.81; DAD group: men, 13.6 ± 4.9 mL/kg vs women, 13.7 ± 4.4 mL/kg; p = 0.94). There was no correlation between EVLW and age in either group (normal lung, R² = 0.006, p = 0.07; DAD, R² = 0.01; p < 0.001).
Among cases with DAD, no difference in EVLW was found between direct injury (13.4 ± 4.2 mL/kg) and indirect injury (14.0 ± 4.9 mL/kg) \( (p = 0.06) \). No difference in EVLW was found between subgroups for indirect injury (i.e., sepsis, 14.1 ± 5.2 mL/kg; multiple-organ failure [MOF], 14.1 ± 4.4 mL/kg; pancreatitis, 12.3 ± 4.8 mL/kg; \( p = 0.07 \)). No significant difference in EVLW was found between patients whose main clinical diagnosis was reported as ARDS (14.1 ± 5.0 mL/kg) and non-ARDS (13.5 ± 4.3 mL/kg) \( (p = 0.17) \).

Figure 4 represents the distribution of calculated EVLW in the normal and DAD groups. A significant difference existed between the normal and DAD groups (normal group, 7.3 ± 2.8 mL/kg vs DAD group, 13.7 ± 4.5 mL/kg; \( p < 0.001 \)).

DISCUSSION
The findings of this study suggest that lungs with DAD are significantly heavier than normal lungs. We also found that an EVLW value greater than 9.8 mL/kg represented the quantitative discriminating threshold for the diagnosis of DAD, whereas an EVLW value greater than 14.6 mL/kg identified DAD patients with 99% certainty. These thresholds for EVLW values may constitute the first validated quantitative bedside diagnostic tool for DAD.
Organ weight is one of the criteria regularly used by pathologists to examine tissues during an autopsy. Lung weight is a classic pathological marker of pulmonary congestion and edema. Petty (2), one of the pioneers in this field, described ARDS lungs as being heavy (>1,000 g) and airless and sinking in water on pathological examination. A recent landmark clinical study by Gattinoni et al (37), in which lung weight was measured using a CT scan, showed that the mean total lung weight was 1,500 ± 506 g in 68 patients with ARDS. Similar lung weight results have also been reported in ARDS autopsy studies (13, 23). These results are similar to those of this study and suggest that heavy lung weight must be a pathological feature of DAD and ARDS.

The panel that established the Berlin criteria also agreed that the morphological hallmarks of ARDS include DAD and increased lung weight (17). The data mentioned in the Berlin criteria suggest that lung weight, estimated by CT scan, correlates significantly with the severity of the injury. The mild, moderate, and severe stages of ARDS were characterized by increased mean lung weight on CT scan (1,371 g; 95% CI, 1,268–1,473; 1,556 g; 95% CI, 1,474–1,638; and 1,828 g; 95% CI, 1,573–2,082; respectively [17]). These stages also correlate with the mortality, duration of mechanical ventilation, and degree of shunt (17). Therefore, quantitative diagnosis of lung weight appears to be of key importance. However, it is not possible to perform CT scans at the bedside or repeatedly without exposing patients to radiation.

The most reliable feature of ARDS is the development of DAD, leading to the accumulation of water in the lungs, which we designate as EVLW. Therefore, EVLW may be the key “bridge” for pathologic-clinical correlation. This value can be easily, quickly, and repeatedly measured at the bedside with robust validation (21–23). Transpulmonary thermodilution can detect small changes in EVLW content (38). EVLW correlates with the level of the biological mediator (39, 40), predicts progression to ARDS in patients with increased risk (41), indicates patient prognosis (34, 36, 42–46), and is clinically useful for assessing the efficacy of therapy (26, 27, 47, 48) without increasing the risk of complications (49). For these reasons, EVLW was chosen in this study as the first validated quantitative bedside diagnostic tool for DAD.

Our previous autopsy study showed that a definite correlation exists between EVLW measured by the transpulmonary thermodilution methods and lung weight in the clinical setting independent of illness, sex, degree of lung injury, amount of pleural fluid, and degree of cardiac output (23). In this study, we found that both normal and DAD lungs of male patients were heavier than those of female patients. This gender gap in lung weight was previously reported in a textbook (normal lungs; men, 850 g vs women, 750 g (6)), with the data being similar to those in this study (normal lungs; men, 860 g vs women, 638 g). However, in this study, no significant difference was observed between sexes by indexing EVLW according to predictive body weight (men, 7.4 ± 2.9 mL/kg vs women, 7.4 ± 3.1 mL/kg; p = 0.81). In addition, this study suggests that there is no relationship between EVLW and age. This study also indicates that although EVLW is increased in all causes of DAD, there are no significant differences between the direct (e.g., pneumonia) and indirect (e.g., sepsis, MOF, or pancreatitis) causes of EVLW in DAD. We, therefore, believe that EVLW indexed by predictive body weight can be used for both interpatient assessment (i.e., comparison with the normal range) and intrapatient assessment (comparison of changes over time in the same patient) regardless of age, gender, or causes of the patients’ diseases.

Data analysis in this study determined that EVLW >9.8 mL/kg statistically discriminates between lungs with DAD and normal lungs, with 81.3% sensitivity and 81.2% specificity. This value was similar to that of the previously proposed or regarded value of pulmonary edema (EVLW > 10 mL/kg) in several clinical studies (9, 32, 33, 41, 50, 51). Furthermore, EVLW >14.6 mL/kg diagnosed DAD with 99% positive predictive value in this study. Interestingly, this value is similar to the value reported by Eisenberg et al (43), who found in their prospective clinical study that patients with an initial EVLW of greater than 14 mL/kg had a significantly greater mortality rate than those with EVLW of less than 14 mL/kg. This value also closely corresponds to the value of 14.3 mL/kg associated with increased mortality in a large retrospective study by Sakka et al (44). Furthermore, recent studies by Phillips et al (36) and Craig et al (34) reported that an EVLW value of 16 mL/kg predicted intensive care unit mortality in patients with ALI/ARDS. Although further studies are needed to validate these results, our quantified pathological definition of DAD has important clinical implications.

However, as suggested by the panel for the Berlin definition (17, 28), we cannot differentiate two pulmonary edemas, cardiogenic and noncardiogenic, by EVLW only. Because cardiogenic (hydrostatic) pulmonary edema will also cause the EVLW to increase (3, 21, 51), cardiogenic causes must be excluded when EVLW greater than 9.8 mL/kg is used for the diagnosis of ARDS. Findings of recent studies suggest that evaluation of the pulmonary vascular permeability index, which can be obtained concurrently with EVLW using transpulmonary thermodilution, is able to differentiate between cardiogenic and noncardiogenic pulmonary edema (i.e., higher pulmonary vascular permeability index values are reported in patients with noncardiogenic pulmonary edema than in patients with cardiogenic pulmonary edema (40, 51, 52)). Although further clinical studies are required to confirm this, patients with EVLW greater than 9.8 mL/kg and high pulmonary vascular permeability index may be typical for ARDS.

This study has several limitations. First, among those who had been pathologically diagnosed with DAD in this study, detailed clinical characteristics of ARDS (e.g., patient clinical course, laboratory and radiographic data, and whether patients had been in the ICU or mechanically ventilated) were not recorded in the autopsy database (31) and thus were not available to us. Without this information, it is difficult to evaluate the clinical relevance directly from the results; therefore, the
number of patients with a clinical diagnosis of ARDS according to the AECC or the Berlin definition could not be confirmed. Other conditions can lead to histopathologic DAD, and they do not all represent the clinical syndrome of ARDS (i.e., oxidative stress and systemic inflammation with permeability-induced pulmonary edema). DAD may be present in various non-ARDS conditions, including acute interstitial pneumonia, bronchiolitis obliterans, organizing pneumonia, and even certain interstitial lung diseases, such as connective-tissue–related diseases. However, most cases of DAD in this study were due to pneumonia, sepsis, or MOF, which are known to be risk factors for ARDS (9, 17).

Second, ARDS is composed of exudative, proliferative, and fibrictive phases (6, 8), and the amount of lung water must be different between each phase. The presence of advanced stages of ARDS with fibrosis should be considered, especially when nonsurvivors are analyzed. In addition, the magnitudes of alveolar or interstitial edema and the extension of hyaline membranes are not the same with regard to weight. However, we could not compare those differences because of the lack of detailed data in the data bank (31).

Third, we used data from the Statistics of Japan to obtain the height to estimate predictive body weight for cases with DAD because actual height was not reported in the “Annual of Pathological Autopsy Cases of Japan” data bank (31) (details in the supplemental data, Supplemental Digital Content 1, http:// links.lww.com/CCM/A654).

Fourth, although three original studies have shown linear relationships between lung weight and EVLW (22, 23, 32), the regression equation used to calculate the EVLW from the actual lung weights is based on data obtained from only 30 patients (23). In addition, lung weight includes the blood content of the lung and, hence, the water in the intravascular compartment (plasma). Because lung weight can increase if pulmonary blood volume increases and because EVLW, by definition, does not include intravascular water, pulmonary blood volume and its hematocrit may affect the relationship between lung weight and EVLW measured by thermodilution.

Finally, although we performed a nationwide large-database study, it was a retrospective single-nation autopsy study. The data in this study were measured in Japanese patients, who have a characteristically small body habitus. Because EVLW was indexed for predicted body weight, which is related to height and lung volumes (35, 53), we believe that our findings can be extrapolated to non-Asian populations. However, multicenter multination prospective clinical studies are required for the validation of an EVLW value acceptable for incorporation into a clinical definition.

CONCLUSIONS
In conclusion, this retrospective analysis of a nationwide autopsy database suggests that significant lung weight differences between normal lungs and lungs with DAD may correspond to an increase in EVLW. EVLW could be used at the bedside to diagnose DAD, and the best EVLW cut-off value to discriminate between normal lungs and lungs with DAD is around 10 mL/kg.

ACKNOWLEDGMENTS
We acknowledge the patients whose bodies were donated for autopsy and their families. We are grateful to Prof. Tomoyuki Kawada for assistance during the statistical review of the article.

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