Anesthesiology 2005; 102:574–80

Increased Pulmonary Venous Resistance Contributes to Increased Pulmonary Artery Diastolic–Pulmonary Wedge Pressure Gradient in Acute Respiratory Distress Syndrome

Charles Her, M.D., Szabolcs Mandy, M.D.,† Mosses Bairamian, M.D.**

Background: **Pulmonary artery diastolic (PAD)–pulmonary wedge pressure (PWP) gradient has been shown to be increased in sepsis and acute respiratory distress syndrome (ARDS). Because pulmonary venous vasoconstriction induced by endotoxemia in sepsis or postcapillary leukocyte aggregation in ARDS or both can increase pulmonary venous resistance (Rpv), it is possible that the elevated Rpv increases PAD-PWP. The authors examined this possibility by assessing the correlation between Rpv and PAD-PWP gradient in patients with ARDS.**

Methods: **Included were 20 patients with ARDS who required surgical procedures during general anesthesia. Rpv was calculated as the difference between mean pulmonary artery (PA) output pressure and PWP divided by cardiac index. Mean PA output pressure was computed from harmonic form of the recorded PA pressure by applying an attenuating factor to its phasic components, for which Fourier analysis was used. Total pulmonary vascular resistance (TPVR) was calculated as the difference between mean PA input pressure and PWP divided by cardiac index. To avoid the effect of PA resistance on TPVR and Rpv, the relative pulmonary venous resistance (Rpv/TPVR) was used.**

Results: **There was a good correlation between Rpv/TPVR and PAD-PWP gradient ($R^2 = 0.698$, $P < 0.0001$). When patients were classified into two groups based on PAD-PWP gradient, the Rpv/TPVR was 0.66 ± 0.06 in the group with a PAD-PWP gradient of 6 mmHg or greater and 0.46 ± 0.08 in the other group ($P < 0.0001$).**

Conclusion: **A strong correlation between Rpv/TPVR and PAD-PWP gradient suggests that the increased Rpv contributes to increased PAD-PWP gradient in patients with ARDS.**

PREVIOUS studies have shown that pulmonary artery diastolic (PAD)–pulmonary wedge pressure (PWP) gradient is increased in sepsis and acute respiratory distress syndrome (ARDS).[1,2] An increase in PAD-PWP gradient has been shown to be associated with high mortality in sepsis[3] and severe acute respiratory failure.[4,5] Therefore, PAD-PWP gradient could be a prognostic indicator in patients with sepsis or ARDS. However, it is not clear what causes increases in the PAD-PWP gradient in these patients. To produce a pressure gradient between the pulmonary artery (PA) and left atrium during diastole, resistance to blood flow distal to the PA, pulmonary capillary, or pulmonary vein should be increased. During the early stage of sepsis or ARDS, before pulmonary capillary remodeling takes place, the increased pulmonary venous resistance (Rpv) should be responsible for increases in the PAD-PWP gradient.

A great deal of evidence indicates that Rpv is increased in ARDS. Previous studies have shown that endotoxemia induces pulmonary venous vasoconstriction, resulting in increases in total pulmonary vascular resistance (TPVR) and relative pulmonary venous resistance.[6,7] Leukocyte aggregation in pulmonary postcapillary venule,[8] which is a prominent feature of the early stage of ARDS, increases Rpv.[9,10] In most cases, probably both pulmonary venoconstriction and postcapillary leukocyte aggregation exert their effects together on Rpv.[11] Taken together, it is most likely that the increased Rpv increases the PAD-PWP gradient in sepsis and ARDS.

In this study, this hypothesis was tested by examining the association between Rpv and PAD-PWP gradient in patients with ARDS. We used an estimated PA output pressure to calculate Rpv. The estimated PA output pressure has been used previously.[12] We predicted that there would be a good correlation between relative pulmonary venous resistance and PAD-PWP gradient. If so, one might be able to use an increase in PAD-PWP gradient as an index of severity of pulmonary venoconstriction or pulmonary leukocyte aggregation in sepsis and ARDS.

Materials and Methods

Included were 20 patients with ARDS who required surgical procedures during general anesthesia. This study was approved by the Committee for Protection of Human Subjects, Office of Research Administration, New York Medical College, Valhalla, New York, with a waiver of the informed consent. The patient group consisted of 11 men and 9 women, ranging in age from 20 to 67 yr (mean age, 50 yr). ARDS followed sepsis in 8 patients, trauma in 6, major surgery in 2, acute necrotizing pancreatitis in 2, and others. All patients had acute hypoxic type of respiratory failure (ratio of partial pressure of oxygen in arterial blood/inspired oxygen concentration in fraction [Pa_{O_2}/F_{IO_2}] < 200) necessitating mechanical ventilatory support with positive end-expiratory pressure. Some other definitions of ARDS in patients included in this study include acute onset of illness, bilateral infiltrates on chest radiography, and PWP less than 18 mmHg. Patients who had had sepsis or ARDS for more than 5 days were not included. All pa-

* Associate Professor, † Assistant Professor.

Received from the Department of Anesthesiology, New York Medical College, Valhalla, New York. This work was done in the Department of Anesthesiology, Westchester Medical Center, Valhalla, New York. Submitted for publication August 6, 2004. Accepted for publication November 17, 2004. Support was provided solely from department and/or institutional sources.

Address reprint requests to Dr. Her: Department of Anesthesiology, Westchester Medical Center, Valhalla, New York 10595. Address electronic mail to: charles6133@aol.com or charles6133@msn.com.

tients had a PA catheter and a radial arterial line in place. No patient was considered for study if there was a history of chronic obstructive pulmonary disease or left ventricular failure. No patient was receiving vasodilators or vasopressors at the time of the study.

Pulmonary artery pressures were measured with transducers (Baxter Healthcare, Santa Ana, CA) at the end of expiration[13] and were corrected for the frequency and phase response. A 7.5-French VIP thermodilution PA catheter with a natural frequency of 33 Hz was used. The effect of frequency and phase response on the amplitude response and phase lag of the manometer–catheter system, which we used in this study, has been described in detail previously.[12] Modulus and phase angle derived from Fourier coefficients were corrected in accordance with the measured amplitude response and phase response of the pressure-measuring system before they were applied. With an ASYST-based fast Fourier transform program, the analysis automatically included up to the 64th harmonic. Cardiac output was determined by the thermodilution technique in triplicate.

Pulmonary venous resistance was calculated as the difference between mean PA output pressure (pulmonary arteriolar pressure or pulmonary capillary pressure) and PWP divided by cardiac index. Relative pulmonary venous resistance (Rpv/TPVR) was calculated as the ratio of Rpv over TPVR. TPVR was calculated as the difference between mean PA pressure (PA input pressure) and PWP divided by cardiac index.

Pulmonary arterial resistance (Rpa) was calculated as the difference between mean PA input pressure and mean PA output pressure divided by cardiac index. The PAD-PWP gradient was calculated as the difference between PA diastolic pressure and PWP. To calculate Rpv, PA output pressure must be obtained. PA output pressure was computed from the harmonic form of the recorded PA pressure by applying an attenuating factor to its phasic components,[12] for which Fourier analysis was used. The viscoelastic property of the PA causes damping of the propagating pulse waves, resulting in an attenuation of the amplitude of the waves and a change in the phase angle. Damping decreases the magnitude of the modulus and the angle of the harmonic form of the PA pressure wave in terms of Fourier coefficients. The attenuating factor, which was used to derive the decreased moduli due to damping, was obtained from a previous human study[14] in which decreases in magnitude of modulus, as a forward transmission ratio (amplitude of pulmonary vein wedge pressure as a percentage of amplitude of the PA pressure), were measured at the frequencies of the harmonics in subjects with and without various degrees of pulmonary hypertension. The transmission ratio was found to vary depending on the frequencies of the harmonics (appendix). The decreased angle, which is the phase angle of PA output pressure,

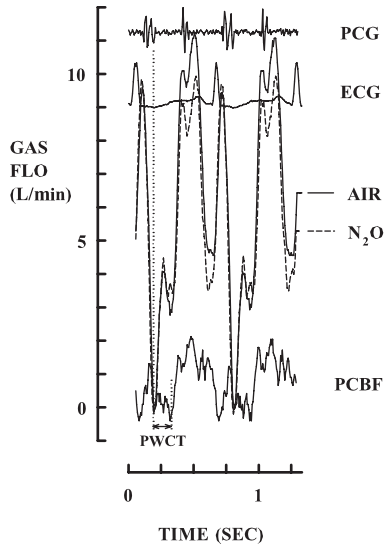

Fig. 1. A whole cycle of pulmonary capillary blood flow (PCBF) tracing (not smoothed), demonstrating the measurement of pulmonary artery pulse wave conduction time (PWCT). ECG = electrocardiogram; N_2O = nitrous oxide; PCG = phonocardiogram.

was calculated by subtracting the change of the angle. The decreased angle is as follows:

$$\omega t + \varphi - \kappa \cdot \delta$$

where ω is the angular velocity, t is time, φ is the phase angle, and κ is the rate of change of the angle with distance δ. Because κ is the same as the ratio of the ω to pulse wave velocity v,[15] and the distance (mean PA length) is the product of v and pulse wave conduction time,[16] the change of angle is as follows:

$$\kappa \cdot \delta = \omega/v \times (v \times Ct) = \omega \times Ct$$

where Ct is PA pulse wave conduction time. The PA pulse wave conduction time (PWCT in fig. 1), which is necessary to obtain the change of angle, was derived from the mean PA pressure by the approach suggested previously.[17] The attenuated Fourier moduli and the decreased angle of harmonic form of PA pressure curve were then computed to synthesize the PA output pressure curve, from which mean PA output pressure was obtained. To avoid beat-to-beat variability, all of the measurements were repeated four times on four different pressure curve tracings and averaged. The data calculation and Fourier analysis have been described previously in detail.[12]

Because the derivation of decreased angle in the current study was based on the PA pulse wave conduction time that was calculated from the mean PA pressure,[17] we also measured the PA pulse wave conduction time from the instantaneous pulmonary capillary blood flow curve and compared it with the calculated value to examine the validity of the previous data.[17] The PA pulse wave conduction time was measured as the interval between the third major vibration of the first heart

sound and the foot of the pulmonary capillary flow pulse (fig. 1).[17] To obtain instantaneous pulmonary capillary blood flow, we used the nitrous oxide–airway–pneumotachographic method. During apneic period after a breath of either air (or oxygen) or nitrous oxide, the pulmonary capillary pulsation produces a pulsatile gas flow. With inhalation of soluble nitrous oxide (60 to 80%), as the pulmonary capillary blood takes up nitrous oxide, alveolar gas pressure decreases and attenuates the pulsatile gas flow.[18,19] Subtraction of the gas flow tracing during apnea after inhalation of nitrous oxide from that after air or oxygen produces a pulsatile waveform of pulmonary capillary blood flow pulse. To obtain a whole cycle of the pulmonary capillary blood flow curve, the gas flow tracing within the period of two consecutive R-R intervals of the electrocardiogram was taken for a whole cycle, six different cycles were averaged, and the averaged gas flow tracing after nitrous oxide inhalation was superimposed over that on air during apnea for subtraction as shown in figure 1. Curve tracings of gas flow, electrocardiograph (lead II), PA pressure, and phonocardiograph were recorded simultaneously on magnetic tape using a 12-bit analog-to-digital converter. Corrections for phase lag of the pneumotachographic system (20 ms) and phase lag from the alveoli to the mouth (4 ms) were applied.

In the operating room, ventilation was supported with a volume-controlled anesthesia ventilator. With the use of a D-lite adapter, the distal end of the side arm spirometry of a Capnomac Ultima monitor (Datex-Ohmeda, Madison, WI), which was placed between the endotracheal tube and breathing circuit, a routine breath-to-breath spirometry monitoring was used throughout the procedure. For the measurement of gas flow, the proximal end of the side arm spirometry tubing was redirected temporarily from the Capnomac Ultima monitor to the pneumotachograph. In no case was any part of the airway or breathing circuit disconnected for the measurement of gas flow. No patient received positive end-expiratory pressure higher than 10 cm H_2O during the study. The anesthetic technique and ventilator settings were chosen for optimum patient care without regard for this study.

After induction of anesthesia, the gas flow was measured during an end-expiratory pause or a short apneic period. Then, nitrous oxide (67%) was started for anesthesia. Approximately 20 s later, the gas flow was measured again. For the rest of anesthesia maintenance, the nitrous oxide concentration was adjusted to maintain oxygen saturation higher than 96% by pulse oximetry. The concentration of inspired nitrous oxide was measured with a mass spectrometer to confirm that an inspired concentration of nitrous oxide was higher than 60%. It is well known that during the first 15–20 min after inhalation of 60% nitrous oxide is started, alveolar concentration of oxygen becomes 52% (not 40%) because of the second gas effect.[20] Therefore, there was no chance that any patients could have received a lower inspired oxygen concentration for this study.

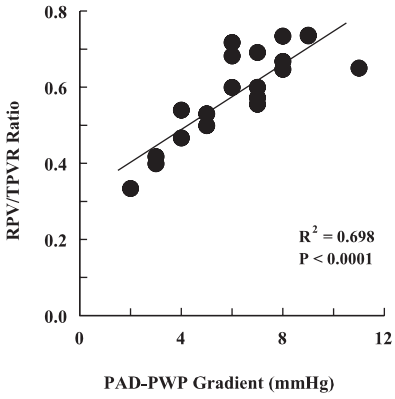

Fig. 2. A linear relation between relative pulmonary venous resistance (ratio of pulmonary venous resistance over total pulmonary vascular resistance [Rpv/TPVR]) and pulmonary artery diastolic (PAD)–pulmonary wedge pressure (PWP) gradient. The equation of the relation line is Rpv/TPVR = 0.043 × PAD-PWP gradient + 0.317.

To determine which hemodynamic data other than the increased Rpv may have contributed to the PAD-PWP gradient, patients were classified into two groups, those patients with a PAD-PWP gradient of greater than 6 mmHg, and those with a PAD-PWP gradient of less than 6 mmHg. A PAD-PWP gradient higher than 6 mmHg has been considered to indicate pulmonary hypertension.[3,5]

The method of least squares was used for regression. To determine whether the fitted model of regression was correct, we examined the residuals from the regression by plotting the residuals against the fitted values ($\hat{y}$).[21] To detect a certain type of serial correlation, the correlation between observational errors, we used the Durbin–Watson test at the level $2\alpha = 0.02$.[22] Regression analysis was used to compare the data by the two different methods for the PA pulse wave conduction time, and the agreement between the two methods was assessed by Bland–Altman analysis.[23] The Student *t* test was used to compare paired data. A two-tailed *P* value less than 0.05 was considered significant.

Results

There was a linear relation between Rpv/TPVR and PAD-PWP gradient as shown in figure 2. The slope with an SE of the estimate was 0.043 ± 0.007 ($R^2 = 0.698$, $P < 0.0001$). When the residuals were examined by plotting against the fitted value ($\hat{y}$), the residuals were randomly scattered, indicating that the errors were independent. There was no serial correlation (Durbin–Watson d-statistic was 1.523).

There was a somewhat weak correlation between Rpv and PAD-PWP gradient. The slope with an SE of the estimate was 16 ± 6 ($R^2 = 0.305$, $P = 0.012$). Analysis of

Table 1. Hemodynamic Data in Patient Group

Variable	Group with PAD-PWP Gradient ≥ 6 (n = 13)	Group with PAD-PWP Gradient < 6 (n = 7)	*P* Value
PAD-PWP gradient, mmHg	8 ± 1	4 ± 1	
Age, yr	49 ± 17	53 ± 14	
Heart rate, beats/min	96 ± 15	87 ± 18	
CI, $l \cdot min^{-1} \cdot m^{-2}$	4.3 ± 1.3	4.5 ± 1.0	
MPAP, mmHg	29 ± 4	26 ± 5	
MPAOP, mmHg	24 ± 3	19 ± 5	0.005
PWP, mmHg	15 ± 3	12 ± 3	
TPVR, $dyn \cdot s \cdot cm^{-5}$	295 ± 101	263 ± 72	
Rpa, $dyn \cdot s \cdot cm^{-5}$	102 ± 41	142 ± 38	
Rpa/TPVR	0.34 ± 0.06	0.55 ± 0.08	< 0.0001
Rpv, $dyn \cdot s \cdot cm^{-5}$	195 ± 67	121 ± 43	0.018
Rpv/TPVR	0.66 ± 0.06	0.46 ± 0.08	< 0.0001
Po_2/Fio_2	191 ± 27	180 ± 60	

CI = cardiac index; MPAP = mean pulmonary artery pressure; MPAOP = mean pulmonary artery output pressure; PAD-PWP gradient = pulmonary artery diastolic–pulmonary wedge pressure gradient; Po_2/Fio_2 = ratio of oxygen tension over inspired oxygen concentration; PWP = pulmonary wedge pressure; Rpa = pulmonary artery resistance index; Rpv = pulmonary venous resistance index; TPVR = total pulmonary vascular resistance index.

Data are presented as mean ± SD.

residuals showed that the errors were independent and there was no serial correlation (Durbin–Watson d-statistic was 2.177). Also, there were good correlations between TPVR and Rpv ($R^2 = 0.77$, $P < 0.0001$) and between TPVR and Rpa ($R^2 = 0.41$, $P = 0.006$), indicating that both the increases in Rpv and Rpa, respectively, contribute to increases in TPVR. However, there was no correlation between Rpa and PAD-PWP gradient.

In table 1, all of the hemodynamic data were compared between two groups, those with a PAD-PWP gradient of 6 mmHg or greater and those with a PAD-PWP gradient of less than 6 mmHg. There was no difference in mean PA pressure or PWP, but mean PA output pressure was much higher in the group with a high PAD-PWP gradient. There was no difference in TPVR, but Rpv/TPVR and Rpv were much higher and Rpa/TPVR was much lower in the group with a high PAP-PWP gradient. There was no difference in Pao_2/Fio_2 between the two groups, suggesting that the severity of pulmonary edema was not different. There was no difference in other hemodynamic data between the two groups. Also, there was no difference in ventilator settings or the use of positive end-expiratory pressure between the two groups. There was no difference in pathology responsible for ARDS between the two groups.

There was a strong correlation between the measured and estimated PA pulse wave conduction times. The slope with an SE of the estimate was 1.008 ± 0.084 ($R^2 = 0.888$, $P < 0.0001$). When the residuals were examined by plotting against the fitted value ($\hat{y}$), the residuals were randomly scattered, indicating that the errors were independent. There was no serial correlation (Durbin–Watson d-statistic was 1.766). To compare two methods (estimated and measured) for agreement, a Bland–Altman analysis was applied. In figure 3, differences in two values of PA pulse wave conduction time were plotted against the average of two values of PA pulse wave conduction time. The mean difference was 0.0011 s, with a 95% confidence interval of −0.0033 to 0.0055. The SE of the 95% limits of agreement was 0.0036 s. The limits of agreement were −0.0175 and 0.0197, which were small enough that the estimated PA pulse wave conduction time could be used in place of the measured value.

There was no episode of hypoxia or hypercapnia during the study. For the combined groups, the mean TPVR was 284 ± 91 $dyn \cdot s \cdot cm^{-5}$, the mean Rpv/TPVR was 0.59 ± 0.12, the mean PAD-PWP gradient was 6 ± 2 mmHg, the mean PA (input) pressure was 28 ± 5 mmHg, the mean PA output pressure was 22 ± 5 mmHg, the mean PWP was 14 ± 3 mmHg, and the mean ratio of Pao_2/Fio_2 was 187 ± 40 mmHg.

Discussion

Previous studies have shown that a PAD-PWP gradient is increased in sepsis and ARDS.[1,2] For the PAD-PWP gradient to be increased, pulmonary vascular resistance distal to the PA should be increased. Because Rpv has

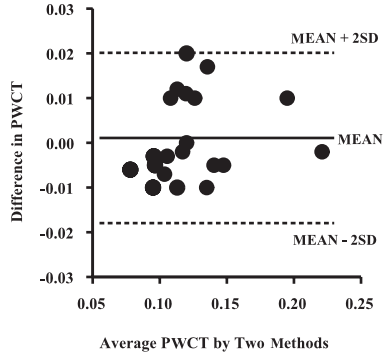

Fig. 3. Bland-Altman analysis for assessing agreement between two methods (the measured and the estimated) to obtain pulmonary artery pulse wave conduction time (PWCT).

been shown to be increased in sepsis and ARDS,[6,9] it is most likely that the elevated Rpv increases the PAD-PWP gradient. In this study, this hypothesis was examined by assessing a correlation between Rpv/TPVR and PAD-PWP gradient in patients with ARDS. The study documented a strong correlation between Rpv/TPVR and PAD-PWP gradient, suggesting that the increased Rpv does contribute to an increase in PAD-PWP gradient in patients with ARDS.

In the current study, we computerized not only data analysis but also sampling and measurement. In processing a Fourier analysis, the number of samples that must be taken is determined by the frequencies present in the record and the number of harmonic to be determined. Also, the measurement accuracy of the ordinates of the samples taken is a limiting factor for the possible accuracy of the analysis. With an analog-to-digital converter, the limit would seem to be set by the number of bits available in the conversion.[24] Therefore, the 12-bit converter used in the current study would increase the accuracy to 0.02% of the width of the channel. The accurate measurement of ordinates also increases the accuracy in measuring the phase angle of the higher harmonics. With this accurate sampling technique, it was considered that there was nearly no sampling error for the Fourier analysis. The sample variance, if any, was attributed to beat-to-beat variability.

During positive-pressure ventilation with positive end-expiratory pressure, intravascular pressure measurement can be affected by positive intrapleural pressure. Therefore, transmural pressure should be calculated to correct the effects of positive end-expiratory pressure on the measurement of pulmonary vascular pressure. However, in calculating transmural pressure (with the assumption that positive pressure is evenly applied to all intrathoracic structures), intrapleural pressure can be deleted from the calculation, particularly when the difference in two pulmonary vascular pressure points is calculated. Therefore, failure to measure intrapleural pressure and to calculate transmural pressure does not affect the calculation of pulmonary vascular resistance.

The calculation of Rpv requires PA output pressure. In a previous study in which pulmonary capillary pressure was estimated by zero time extrapolation of the slow component of the arterial occlusion profile (PA pressure occlusion profile), Rpv/TPVR was the same among the patients with acute respiratory failure regardless of severity of lung involvement.[25] Rpv/TPVR in those patients with severe acute respiratory failure was 0.42, which was not much different from the normal value (0.4).[26]

With the same technique to estimate pulmonary capillary pressure, others have failed to demonstrate the evidence of pulmonary venoconstriction during endotoxemia in domestic pigs.[27] Because the PA pressure occlusion profile overestimates pulmonary capillary pressure,[28] Rpv/TPVR would have been expected to be increased in those two previous studies. Conversely, using the PA pressure occlusion profile, an animal study has shown that endotoxin increases relative pulmonary venous resistance.[7] However, a theoretical analysis of occlusion profile techniques has indicated that the PA pressure occlusion profile overestimates and the pulmonary venous pressure occlusion profile underestimates pulmonary capillary pressure.[28] In addition to the theoretical problems with PA pressure occlusion profile, some methodologic and technical problems may influence the interpretation of data.[9] The PA occlusion pressure measurements are influenced by the instant at which occlusion occurs during cardiac cycle, due to the pulsatility of pressure in the pulmonary capillary bed or due to artifacts generated by catheter movements during balloon inflation. The abrupt discontinuation of mechanical ventilation used in some studies[25] to facilitate the measurement can induce significant changes in pulmonary hemodynamics and vascular resistances. In fact, this simplified model of occlusion profile has been considered inaccurate.[9]

In other studies, when peripheral pulmonary venous pressure was measured, Rpv was increased. A previous report has shown that with the use of a deflated PA catheter that is wedged in a small artery of West zone 3 of the lung, the pressure measured is that of a small vein.[29] Using this technique, others have reported that during endotoxemia in unanesthetized sheep, Rpv/TPVR increases from 0.3 to 0.6, indicating intense pulmonary venoconstriction.[6] With the same technique to measure the peripheral pulmonary venous pressure, a previous study has shown that Rpv/TPVR is increased in patients with ARDS.[9] In that study,[9] however, Rpv/TPVR was only 0.275 in ARDS and was the same as the value in cardiac failure. With a regular PA catheter in wedge position, they measured the medium pulmonary vein resistance, not the small vein resistance, resulting in underestimation of the Rpv/TPVR, particularly in ARDS.

In the current study, using Fourier analysis, we estimated PA output pressure from the harmonic form of PA pressure by applying an attenuating factor, transmission ratio, to its phasic components. We defined PA output pressure used in the current study as pulmonary arteriolar pressure or pulmonary capillary pressure (these two pressures should be close or identical). The possible limitation of estimating PA output pressure in the current study is the use of an attenuating factor, a transmission ratio, which was obtained from the other study.[14] However, when a different attenuating factor, which was obtained by a different method in the other previous study,[30] was used to estimate PA output pressure, the value of PA output pressure was the same as the value measured with the attenuating factor used in the current study.[12] The absence of difference in these two values supports the validity of estimation of PA output pressure

in the current study. Moreover, to estimate PA pressure from pulmonary vein wedge pressure, a previous study has shown that when mean PA pressure is higher than 20 mmHg, discrepancy between mean PA pressure and mean pulmonary vein wedge pressure increases but can be corrected by adding the diastolic pulmonary vein wedge–left atrial pressure gradient to the mean pulmonary vein wedge pressure.[31] To repeat their steps, we added the PAD-PWP gradient to the PA output pressure to estimate the mean PA pressure and compared this estimated mean PA pressure with the measured value. There was no difference in the two values of mean PA pressure (paired *t* test, $P = 0.48$). This finding can be explained by a longitudinal distribution of vascular resistance in the pulmonary vascular system.[16] Also, this finding suggests that PA output pressure in the current study may be the same as or close to pulmonary vein wedge pressure, which should read pulmonary arteriolar pressure or pulmonary capillary pressure, providing more support that the estimation of PA output pressure in the current study is valid.

Although PA output pressure was estimated in the current study, mean Rpv/TPVR (0.59) in the current study was comparable with that (0.6) in the previous study.[6] In the group with a high PAD-PWP gradient in the current study, the mean Rpv/TPVR was 0.66 (table 1), which is even higher than that in the previous study,[6] despite no difference in TPVR between the two groups, suggesting that Rpv was increased further by leukocyte aggregation in addition to the endotoxin-induced pulmonary venoconstriction. In the group with a low PAD-PWP gradient, the mean Rpv/TPVR was 0.46, which is close to a normal value. As such, our data based on the estimated PA output pressure are consistent with those in the other study,[6] in which peripheral pulmonary venous pressure was measured.

The strong correlation between PAD-PWP gradient and Rpv/TPVR indicates that an increase in PAD-PWP gradient, which has been shown to be associated with high mortality in sepsis[3] and severe ARDS,[5] is probably due to intense endotoxin-induced pulmonary venoconstriction and progressive leukocyte aggregation. Also, a persistently high PAD-PWP gradient probably indicates an increase in pulmonary capillary resistance due to capillary leukocyte aggregation and capillary remodeling in addition to the increased Rpv. However, because we did not measure leukocyte aggregation as a possible cause of the increased PAD-PWP gradient or the increased Rpv/TPVR in the current study, we could only speculate on the effect of leukocyte aggregation on PAD-PWP gradient. Nevertheless, as suggested previously,[3] an important prognostic indicator of the outcome of patients with sepsis and/or ARDS is whether the PAD-PWP gradient increases or persists over time.

In summary, our data indicate that increased Rpv contributes increases in PAD-PWP gradient in patients with ARDS. Because endotoxin-induced pulmonary venoconstriction or postcapillary leukocyte aggregation or both increases Rpv, one may use PAD-PWP gradient as an index of severity of pulmonary venoconstriction or possibly leukocyte aggregation in patients with ARDS.

Appendix: Calculation of PA Output Pressure with Application of Fourier Analysis

The Fourier representation of the pressure pulse can be written

$$PA(t) = PA_0 + \sum_{n=1}^{\infty} (A_n \cos \omega t + B_n \sin \omega t) , \quad (1)$$

which can be rearranged as (because $M_n^2 = A_n^2 + B_n^2$)

$$PA(t) = PA_0 + \sum_{n=1}^{\infty} M_n \cos (\omega t - \Phi_n) , \quad (2)$$

where PA(t) is PA pressure at time t, PA_0 is PA input pressure (mean PA pressure), M_n is modulus, and φ_n is the phase angle of harmonic form of recorded PA pressure at nth harmonic, and ω is the angular velocity. The viscoelastic property of PA causes damping of the propagating pulse waves, resulting in an attenuation of the amplitude of waves and a change in the phase angle. Damping decreases the magnitude of the modulus and the angle of harmonic form of PA pressure wave in terms of Fourier coefficients.

1. A decrease in the magnitude of modulus:
The attenuating factor, which is a forward transmission ratio of pulse waves (amplitude of pulmonary vein wedge pressure as a percentage of amplitude of the PA pressure) was applied to derive the decreased modulus as follows:

$$Pa(t) = Pa_0 + \sum_{n=1}^{\infty} m_n \cos \{(\omega t - \Phi_n) - \kappa \cdot \delta\} , \quad (3)$$

where Pa(t) is PA output pressure at time t, Pa_0 is mean PA output pressure, m_n is attenuated modulus, and $\{(\omega t + \varphi_n) - \kappa \cdot \delta\}$ is the decreased angle of harmonic form of PA output pressure at nth harmonic. The transmission ratios are as follows:[14]

When the frequency is between 1 and 2, the ratio is 32.8%.
When the frequency is between 3 and 4, the ratio is 24.8%.
When the frequency is between 4 and 5, the ratio is 46.2%.
When the frequency is between 5 and 6, the ratio is 25.6%.

2. A decrease in the angle:
The decreased angle is as follows[15]:

$$(\omega t + \Phi_n) - \kappa \cdot \delta , \quad (4)$$

where κ is the rate of change of angle with distance δ (mean PA length).

Because κ is the same as the ratio of the ω to pulse wave velocity v and the distance δ is the product of v and pulse wave conduction time,[16] the change of angle is as follows:

$$\kappa \cdot \delta = \omega / v \times (v \times Ct) = \omega \times Ct , \quad (5)$$

where Ct is PA pulse wave conduction time. The PA pulse wave conduction time (PWCT in fig. 1), which is necessary to obtain the change of angle, was derived from the mean PA pressure by the approach suggested previously.[17]

3. Because a value for Pa_0 is needed, the equation was rearranged as

$$Pa_0 = Pa(t) - \sum_{n=1}^{\infty} m_n \cos\{(\omega t - \Phi_n) - \kappa \cdot \delta\}. \quad (6)$$

When t is zero, PA(t) or Pa(t) should be equal to PA diastolic pressure, because diastolic pressures are the same throughout the PA system, including pulmonary capillary.

4. Values for Pa_0, the attenuated modulus (m_n), and the decreased angle $\{(\omega t - \varphi_n) - \kappa \cdot \delta\}$ are applied to equation 3 to resynthesize the PA output pressure curve. Although one can obtain mean PA output pressure from equation 6, it is recommended to resynthesize the PA output pressure curve to confirm that the pressure curve is not distorted and to obtain the mean value.

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