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Increased Pulmonary Venous Resistance in Morbidly Obese Patients without Daytime Hypoxia

Clinical Utility of the Pulmonary Artery Catheter

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ABSTRACT

Background: The pulmonary artery (PA) diastolic-pulmonary capillary wedge pressure (PAD-PCWP) gradient has been shown to be increased in morbidly obese patients without daytime hypoxia. In sepsis, the increased pulmonary venous resistance (PvR) contributes to increases in PAD-PCWP gradient. In addition, the obesity-related endotoxemia is known to be involved in the pathophysiology of metabolic syndrome in obesity. Therefore, it is possible that the increased PvR contributes to increases in PAD-PCWP gradient in morbid obesity. We examined this possibility.

Methods: Included were 25 obese patients without daytime hypoxia undergoing bariatric surgery under general anesthesia. PvR was calculated as the difference between mean PA output pressure and PCWP divided by cardiac index. Mean PA output pressure was computed from the 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 pressure and PCWP divided by cardiac index. To avoid the effect of PA resistance on TPVR and PvR, the PvR/TPVR ratio was used.

Results: There was a good correlation between PvR/TPVR ratio and PAD-PCWP gradient ($r^2 = 0.785$, $P < 0.0001$). When patients were divided into two groups based on PAD-PCWP gradient, the PvR/TPVR ratio was 0.67 ± 0.06 (mean ± SD) in the group with a PAD-PCWP gradient of at least 6 mmHg and 0.48 ± 0.05 in the other group ($P < 0.0001$).

Conclusions: A strong correlation between PvR/TPVR ratio and PAD-PCWP gradient suggests that the increased PvR contributes to increased PAD-PCWP gradient in obese patients without daytime hypoxia.

What We Already Know about This Topic

- Increases in pulmonary arterial or venous resistance can increase the gradient between pulmonary artery diastolic and pulmonary capillary wedge pressure
- Morbid obesity without daytime hypoxia increases this gradient

What This Article Tells Us That Is New

- In 25 morbidly obese patients without daytime hypoxia, pulmonary venous resistance was increased, perhaps because of chronic inflammation associated with obesity
- The pulmonary artery diastolic pressure–pulmonary capillary wedge pressure gradient may indicate the severity of inflammation in morbid obesity

THE hemodynamic disturbances in morbidly obese patients without daytime hypoxia are directly attributable to an increase in the total blood volume. The increased pulmonary blood volume (PBV) due to the increased total body blood volume elevates pulmonary artery (PA) pressure and total pulmonary vascular resistance (TPVR).[1,2] In morbidly obese patients with daytime hypoxia, the increased PBV, combined with changes in respiratory mechanics, contributes to ventilation-perfusion abnormalities,[1,3] leading to increased PA pressure and TPVR[4] and also to increased PA diastolic-pulmonary capillary wedge pressure (PAD-PCWP) gradient.[1] Thus, the increased PBV alone in morbidly obese patients without daytime hypoxia is not expected to increase PAD-PCWP gradient. However, increases in PAD-PCWP gradient have been found in some of morbidly patients with-

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out daytime hypoxia,[5,6] particularly those with depressed right ventricular function.[6]

In patients with acute respiratory distress syndrome or sepsis, an increased pulmonary venous resistance (PvR) has been found to contribute to increases in PAD-PCWP gradient.[7] Pulmonary venous vasoconstriction induced by endotoxemia[8] and leukocyte aggregation in pulmonary postcapillary venules[9] are responsible for the increased PvR. In patients with morbid obesity, the inflammatory reaction induced by a low-grade obesity-related endotoxemia and/or by adipokines released from adipose tissue, which has been shown to be involved in the pathophysiology of metabolic syndrome,[10,11] may be able to increase PvR by activating prostanoid-mediated pulmonary vasoconstriction. If so, the increased PvR should be responsible for increases in PAD-PCWP gradient in morbidly obese patients.

In pulmonary embolism, in which pulmonary arterial hypertension is a main pathophysiology, PAD-PCWP gradient is also increased.[12,13] In high-altitude–induced pulmonary arterial hypertension, the PvR/TPVR ratio (fraction of the TPVR contributed by PvR) has been reported not to be increased, despite the presence of a significant PAD-PCWP gradient.[13] As such, an increase in PvR is not the only condition that is responsible for the increased PAD-PCWP gradient. In this situation, the measurement of PvR with the use of a PA catheter can separate those with an increased PvR from those with an increased pulmonary arterial resistance (PaR). Thus, depending on whether PvR or PaR is increased, therapeutic modality should be different in patients with an increased PAD-PCWP gradient.

In the present study, we tested the hypothesis that the increased PvR is responsible for the increased PAD-PCWP in patients with morbid obesity by examining the correlation between PvR and PAD-PCWP gradient in obese patients without daytime hypoxia. We measured PvR by using an estimated PA output pressure. The estimated PA output pressure has been used previously as a reliable estimate of pulmonary capillary pressure.[7,14] We predicted that an increased PvR would explain increases in PAD-PCWP gradient in these patients.

Materials and Methods

Included were 25 consecutive morbidly obese patients undergoing bariatric surgery under general anesthesia. This study was approved by the Committee of Clinical Investigation, Pusan National University Yangsan Hospital, Gyeongnam, Korea, and the Committee for the Protection of Human Subjects, New York Medical College, New York, New York, and informed consent was obtained from all patients. The patients group consisted of 18 women and 7 men; mean age ± SD was 38 ± 10 yr (ranging from 22 to 59 yr), and mean body mass index ± SD was 58 ± 12 kg/m^2. Five patients had obstructive sleep apnea syndrome requiring a continuous positive airway pressure device during night sleep, but none of these patients had daytime hypoxia. Patients who weighed less than 136 kg were excluded, because invasive monitoring lines were not used for the perioperative care in these less obese patients. Patients with a history of obesity-hypoventilation syndrome with daytime hypoxia were not included, for there were few cases. (Surgeons rarely perform bariatric surgery on these patients.) No patient had a history of chronic obstructive pulmonary disease, uncontrolled systemic hypertension, or left ventricular failure. All patients had preoperative pulmonary function tests to rule out obstructive pulmonary disease, and two-dimensional echocardiography to rule out left ventricular dysfunction and valvular abnormalities.

In the operating room, patients were positioned in reverse Trendelenburg position in an effort to take the weight of the torso off the chest and upper abdomen. The degree of reverse Trendelenburg position varied depending on abdomen size. General anesthesia was induced with midazolam, incremental dose of fentanyl (5 μg/kg), followed by propofol and succinylcholine. After the trachea was intubated, patients were placed in supine or slight head-up position. Desflurane with intermittent doses of fentanyl and atracurium were used for the maintenance of anesthesia. Ventilation was supported with a volume-controlled anesthesia ventilator. A tidal volume of 6–8 ml/kg was maintained with a constant inspiratory flow rate. The rate of controlled ventilation was adjusted to maintain an arterial carbon dioxide tension between 35 and 45 mmHg. Desflurane used in the present study may influence pulmonary vascular resistances, but it does not influence the PvR/TPVR ratio.

PA catheter was inserted for diagnostic and therapeutic purposes immediately after induction of general anesthesia. PA pressures were measured with transducers at the end of expiration and corrected for the frequency and phase responses. A 7.5-French VIP thermodilution PA catheter with a natural frequency of 33 Hz (Baxter Healthcare, Santa Ana, CA) was used. The effects of frequency and phase responses on the amplitude response and phase lag of the manometer-catheter system that we used in this study has been described in detail previously.[14] Modulus and phase angle derived from Fourier coefficients were corrected in accordance with the measured amplitude and phase responses of the pressure-measuring system before they were applied. Cardiac output was determined by the thermodilution technique in triplicate.

PvR was calculated as the difference between mean PA output pressure (pulmonary capillary pressure) and PCWP divided by cardiac index. Relative PvR (*i.e.*, the fraction of the TPVR contributed by PvR) was calculated as the ratio of PvR/TPVR. TPVR was calculated as the difference between mean PA pressure (PA input pressure) and PCWP divided by cardiac index. Pulmonary arterial resistance (PaR) was calculated as the difference between mean PA input pressure and mean PA output pressure divided by cardiac index. To calculate PvR, 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

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phasic components,[7,14] 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 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[15] 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 forward transmission ratio was found to vary depending on the frequencies of the harmonics (appendix). Thus, the forward transmission ratio was applied to modulus of each harmonic form of PA pressure curve with corresponding frequency to derive the decreased modulus.[7] The decreased angle, which is the phase angle of PA output pressure, was calculated by subtracting the change of angle as shown previously (also in appendix).[14] 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 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.[7,14]

Because the derivation of decreased angle in the present study was based on the PA pulse wave conduction time (PWCT), which was calculated from the mean PA pressure, we also measured the PA PWCT from the instantaneous pulmonary capillary blood flow curve and compared with the calculated value to examine the validity of the previous data.[16] The PA PWCT was measured as the interval between the third major vibration of the first heart sound and the foot of the pulmonary capillary blood flow pulse (fig. 1).[16] To obtain instantaneous pulmonary capillary blood flow, we used the nitrous oxide-airway-pneumotachographic method. During apneic period after a breath of either oxygen or nitrous oxide, the pulmonary capillary pulsation produces a pulsatile gas flow. With inhalation of soluble nitrous oxide (60–80%), as the pulmonary capillary blood takes up nitrous oxide, alveolar gas pressure decreases, and attenuates the pulsatile gas flow.[17,18] Subtraction of the gas flow tracing during apnea after inhalation of nitrous oxide from that after oxygen produces a pulsatile waveform of pulmonary capillary blood flow pulse.[7]

The baseline measurement of cardiac output and PA pressure reading were done right after induction of anesthesia before hydration was begun and repeated when patients were considered adequately hydrated, as assessed by PCWP and urine output, to evaluate the effects of changes in PBV on vascular resistance.

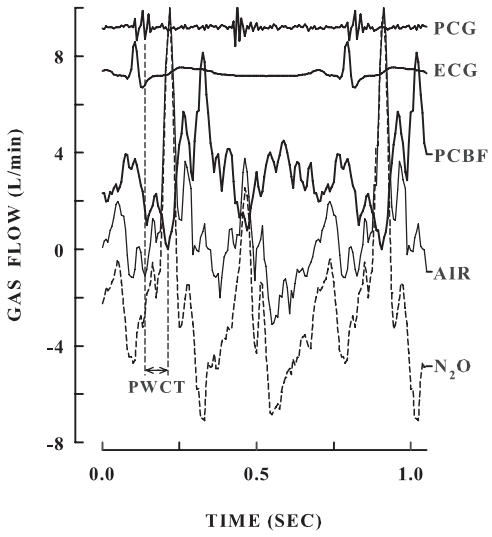

Fig. 1. Measurement of pulmonary artery pulse wave conduction time (PA PWCT). ECG = electrocardiogram; N_2O = nitrous oxide; PCBF = pulmonary capillary blood flow; PCG = phonocardiogram.

To determine which hemodynamic data other than the increased PvR might have contributed to the PAD-PCWP gradient, patients were divided into two groups: those patients with a PAD-PCWP gradient of at least 6 mmHg and those with a PAD-PCWP gradient less than 6 mmHg. A PAD-PCWP gradient of at least 6 mmHg has been considered to indicate pulmonary hypertension.[19]

Statistical Analysis

The method of least squares was used for regression. To determine whether the fitted model of regression is correct, we examined the residuals from the regression by plotting the residuals against the fitted values ($\hat{y}$).[20] In regression analysis, it is typically assumed that the observational errors are pairwise uncorrelated. However, because participants contributed a certain number of scores to the analysis, we might expect that scores within time over the same individual might be more similar than scores selected at random. In other word, scores may be autocorrelated. If there is a first-order autocorrelation in the residuals, doubt is cast on the fitted model, and the data should be reconsidered. A popular test for detecting an autocorrelation is the Durbin-Watson test, which is the *d* statistic. If the value of *d* is not significant, it is then assumed that there is no autocorrelation.[21] We used the Durbin-Watson test at the level of $2\alpha = 0.02$, two-sided equal-tailed test against alternatives.[21] 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.[22] Student's *t* test was used to compare paired data. All data were presented as mean ± 1 SD. A two-tailed *P* value less than 0.05 was considered significant. SYSTAT (Systat Software, Inc., Richmond, CA) statistical software was used for statistical analysis.

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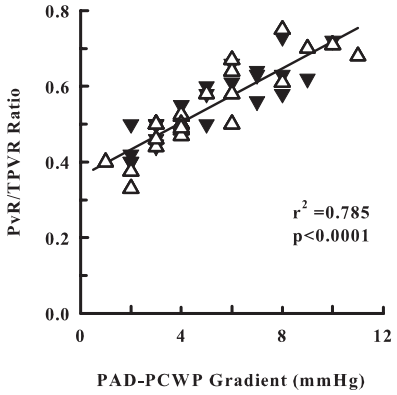

Fig. 2. A linear relationship between pulmonary artery diastolic-pulmonary capillary wedge pressure (PAD-PCWP) gradient and the ratio of pulmonary venous resistance/total pulmonary vascular resistance (PvR/TPVR ratio) as combined data. PvR/TPVR ratio = 0.0357 × PAD-PCWP gradient + 0.365. *Open triangles* represent data at low pulmonary blood volume (PBV; r^2 = 0.798, $P < 0.0001$), and *closed triangles* represent data at high PBV ($r^2 = 0.749$, $P < 0.0001$).

Results

There were linear relationships between the PvR/TPVR ratio and PAD-PCWP gradient both at the baseline and after hydration (fig. 2). At the baseline before hydration was begun (low PBV), the slope with a SE of the estimate was 0.037 ± 0.049 ($r^2 = 0.791$, $P < 0.0001$). The *d* statistic was 1.659, which was not significant, indicating that there was no autocorrelation. After hydration (high PBV) the slope with a SE of estimate was 0.034 ± 0.045 ($r^2 = 0.775$, $P < 0.0001$) (*d* statistic was 1.857, which was not significant). Because there was no difference between two linear relationship lines, two data (data at baseline or at low PBV and data at high PBV) were combined as shown in figure 2. The combined data also yield a strong correlation between the PvR/TPVR ratio and the PAD-PCWP gradient. The slope with a SE of estimate was 0.036 ± 0.046 ($r^2 = 0.785$, $P < 0.0001$) (*d* statistic was 1.743, which was not significant, indicating that there was no autocorrelation). The residuals were randomly scattered, indicating that the errors were independent.

There were good correlations between PvR and PAD-PCWP gradient both at the baseline and after hydration. The slope with a SE of estimates was 23 ± 36 ($r^2 = 0.749$, $P < 0.0001$), and 18 ± 63 ($r^2 = 0.678$, $P < 0.0001$), respectively. In addition, there were good correlations between TPVR and PvR ($r^2 = 0.842$, $P < 0.0001$) and between TPVR and PaR ($r^2 = 0.307$, $P = 0.004$), indicating that the increases in both PvR and PaR, respectively, contribute to increases in TPVR. However, there was no correlation between PaR and PAD-PCWP gradient. These correlations did not change after hydration (table 1).

In table 1, all of the hemodynamic data measured at the baseline (low PBV) were compared with those measured after hydration (high PBV) to determine whether acute volume overload contributes to changes in pulmonary vascular resistance. Higher right ventricular end-diastolic volume index, cardiac index, stroke volume index, mean PA pressure, and mean PA output pressure indicate that hydration increased PBV. However, hydration did not change TPVR, PvR, PvR/TPVR ratio, PaR, or PAD-PCWP gradient, indicating that acute volume overload does not contribute to changes in pulmonary vascular resistance in these obese patients.

Table 1. Hemodynamic Data with Different Pulmonary Blood Volume.

Variable	Low PBV	High PBV	*P* Value
RV EDVI (ml/m^2)	117 ± 25	136 ± 26	<0.0001
RV ESVI (ml/m^2)	74 ± 24	86 ± 26	<0.0001
Heart rate (beat/min)	85 ± 16	84 ± 14	0.464
CI (l · min^{-1} · m^{-2})	3.6 ± 1.0	4.1 ± 0.9	<0.0001
SVI (ml/m^2)	43 ± 10	50 ± 9	<0.0001
MPAP (mmHg)	26 ± 5	32 ± 4	<0.0001
MPAOP (mmHg)	21 ± 5	27 ± 4	<0.0001
TPVR (dyne · s · cm^{-5})	277 ± 78	268 ± 75	0.303
PaR (dyne · s · cm^{-5})	126 ± 32	118 ± 33	0.324
PaR/TPVR	0.47 ± 0.11	0.42 ± 0.07	0.662
PvR (dyne · s · cm^{-5})	151 ± 64	149 ± 57	0.733
PvR/TPVR	0.53 ± 0.11	0.55 ± 0.09	0.55
PCWP (mmHg)	14 ± 4	19 ± 4	<0.0001
RVEF	0.39 ± 0.10	0.38 ± 0.01	0.621
PAD-PCWP gradient	5 ± 3	5 ± 2	0.90

Low and high PBV indicate relative values of pulmonary blood volume before and after hydration, respectively.

CI = cardiac index; MPAOP = mean pulmonary artery output pressure; MPAP = mean pulmonary artery pressure; PAD-PCWP = gradient pulmonary artery diastolic-pulmonary capillary wedge pressure gradient (mmHg); PaR/TPVR = ratio of pulmonary arterial resistance to TPVR; PCWP = pulmonary capillary wedge pressure; PvR/TPVR = ratio of pulmonary venous resistance to TPVR; RV EDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RV ESVI = right ventricular end-systolic volume index; SVI = stroke volume index; TPVR = total pulmonary vascular resistance.

In table 2, all of the hemodynamic data of the two groups were compared (*i.e.*, those with a PAD-PCWP gradient of at least 6 mmHg and those with a PAD-PCWP gradient less than 6 mmHg). There was no difference in mean PA pressure or PCWP in the two groups, but mean PA output pressure was higher in the group with a high PAD-PCWP gradient. TPVR, PvR, and the PvR/TPVR ratio were much higher in the group with a higher PAD-PCWP gradient, indicating that the increased PvR contributes increases in PAD-PCWP gradient. There was no difference in right ventricular end-diastolic volume index or stroke volume index in the two groups, indicating that PBV was not different. In addition, there was no difference in the slope of right ventricular end-systolic pressure-volume relationship line in the two groups, indicating that right ventricular function was not different.

To compare the two methods (estimated and measured) for agreement, a Bland-Altman analysis was used. In figure 3, differences in two values of PA PWCT were plotted against the average of two values of PA PWCT, which showed that there was a good agreement between the two methods. The mean difference was 0.003, and the SE of the bias (difference) was

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Table 2. Hemodynamic Data in Groups with Different PAD-PCWP Gradients

Variable	PAD-PCWP Gradient ≥6 (n = 9)	PAD-PCWP Gradient <6 (n = 16)	*P* Value
PAD-PCWP gradient	8 ± 2	3 ± 1	<0.0001
Age (yr)	40 ± 8	37 ± 11	0.437
Heart rate (beat/min)	89 ± 21	82 ± 12	0.283
BMI (kg/m^2)	54 ± 8	60 ± 13	0.311
CI (l · min^{-1} · m^{-2})	3.7 ± 1.1	3.6 ± 1.0	0.898
SVI (ml/m^2)	42 ± 10	44 ± 11	0.617
MPAP (mmHg)	30 ± 6	27 ± 6	0.266
MPAOP (mmHg)	22 ± 5	20 ± 5	0.214
PCWP (mmHg)	12 ± 6	15 ± 4	0.171
TPVR (dyne · s · cm^{-5})	341 ± 83	241 ± 46	0.0007
PvR (dyne · s · cm^{-5})	220 ± 57	114 ± 23	<0.0001
PvR/TPVR	0.65 ± 0.08	0.47 ± 0.05	<0.0001
PaR	121 ± 37	127 ± 32	0.763
PaR/TPVR	0.35 ± 0.08	0.53 ± 0.06	<0.0001
RV EF	0.37 ± 0.05	0.39 ± 0.11	0.868
RV EDVI	114 ± 27	120 ± 24	0.566
Slope of RV ESPVRL	0.51 ± 0.15	0.55 ± 0.12	0.476

BMI = body mass index; CI = cardiac index; MPAP = mean pulmonary artery pressure; MPAOP = mean pulmonary artery output pressure; PAD-PCWP = gradient pulmonary artery diastolic-pulmonary capillary wedge pressure gradient; PaR/TPVR = pulmonary arterial resistance/TPVR ratio; PvR/TPVR = pulmonary venous resistance/TPVR ratio; RV EDVI = right ventricular end-diastolic volume index; RV EF = right ventricular ejection fraction; RV ESPVRL = right ventricular end-systolic pressure-volume relationship line; SVI = stroke volume index; TPVR = total pulmonary vascular resistance.

0.0015. The SE of the 95% limits of agreement was 0.0026. The 95% confidence interval for the upper limit of agreement was 0.011 to 0.021. The 95% confidence interval for lower limits of agreement was −0.0157 to −0.0049. Considering the fact that the sample size is small, these intervals are reasonably narrow, suggesting a very close agreement of two methods.

No patient had preoperative arterial oxygen saturation lower than 98% by pulse oximetry. There was no episode of hypoxemia or hypercarbia during the study.

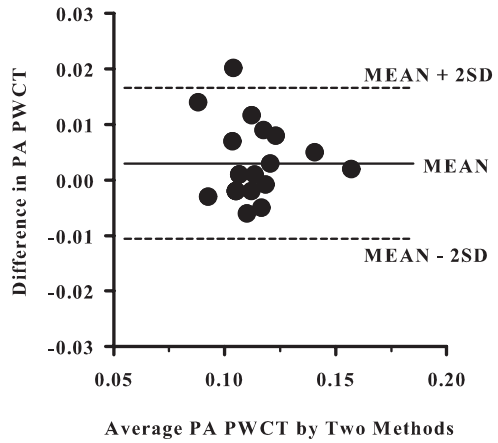

Fig. 3. Comparison of the measured pulmonary artery pulse wave conduction time (PA PWCT) with that estimated by the Bland-Altman method.

Discussion

In patients with acute respiratory distress syndrome or sepsis, the increased PvR has been shown to contribute to increases in PAD-PCWP gradient.[7] However, in morbidly obese patients without daytime hypoxia, the PAD-PCWP gradient is not expected to be increased. Nevertheless, because an increased PAD-PCWP gradient has been found in some morbidly obese patients without daytime hypoxia,[5,6] it is possible that PvR is increased and the increased PvR is responsible for increases in PAD-PCWP gradient in those patients. In the present study, this hypothesis was examined by assessing a correlation between the PvR/TPVR ratio and PAD-PCWP gradient in morbidly obese patients without daytime hypoxia. The study documented a strong correlation between the PvR/TPVR ratio and PAD-PCWP gradient, suggesting that the increased PvR does contribute to an increase in PAD-PCWP gradient in morbidly obese patients without daytime hypoxia.

It is not clear what causes increases in PvR in these patients. The absence of difference in PvR between two different PBVs (table 1) indicates that the increase in PvR is not the result of high PBV. A growing body of evidence has suggested that the mechanism of pulmonary venous vasoconstriction in morbidly obese patients without daytime hypoxia is similar to that in patients with endotoxemia, in which pulmonary venous vasoconstriction is induced by a potent vasoconstrictor, thromboxane A_2.[23] Previous studies have shown that obesity is associated with a low-grade endotoxemia,[24] and obesity also increases prostanoid-mediated vasoconstriction and vascular thromboxane receptor gene expression.[25] Moreover, an animal study has demonstrated that the intestinal mucosal barrier function was significantly impaired in the animal models of obesity because of an abnormal distribution of tight junction proteins, thus favoring translocation of endotoxin.[11] Thus, this endotoxemia, although low grade, can induce inflammatory reaction, contributing to leukocyte, platelet, and endothelial activation *via* the Toll-like receptor 4 complex.[26] In addition, other investigators have found that the coculture of adipocytes and macrophages induces significant release of saturated free fatty acids by adipocytes and significant increases in proinflammatory cytokines from macrophages.[27] The saturated free fatty acids released from adipocytes were capable of activating macrophage nuclear factor-κB in a Toll-like receptor 4–dependent manner.[27] Furthermore, adipose tissue secretes a wide range of cytokines named adipokines and leptin, and adiponectins are the exceptional adipokines that play an important role in obesity-related inflammation. A previous study has shown that adiponectin activates nuclear factor-κB, cytokine release, and messenger RNA expression of inflammatory marker genes in a Toll-like receptor 4–independent manner.[11] Therefore, both Toll-like receptor

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4–dependent (with exogenous agonist such as endotoxin) and Toll-like receptor 4–independent pathways can be operative for induction of inflammatory reaction in patients with morbid obesity. Thus, the increased production of prostanoid induced by this obesity-related inflammatory reaction, in addition to the increased vascular thromboxane receptor gene expression, may well be the mechanism of pulmonary venous vasoconstriction in these patients.

One might argue that PvR could have been increased by hypoxia in the present study, because patients with morbid obesity may experience hypoxia during night sleep even without a definite history of obstructive sleep apnea. However, hypoxic pulmonary vasoconstriction mainly increases PA pressure and PaR, which are reversible during normoxia,[28] although pulmonary venous pressure has been reported to be increased during hypoxia.[29] In that study,[29] hypoxia increased PA pressure by 69%, whereas it increased pulmonary venous pressure by 40%, and the PvR/TPVR ratio decreased, indicating that an increase in PA pressure was a major effect of hypoxic pulmonary vasoconstriction. A hemodynamic study on patients with obstructive sleep apnea has shown that patients with PA hypertension have a high PAD-PCWP gradient (mean, 8 mmHg), thus indicating an increased PvR, whereas patients without PA hypertension have no significant PAD-PCWP gradient.[5] In that study,[5] patients in neither group had daytime hypoxia, but patients with PA hypertension had a higher body mass index (mean, 37 kg/m^2) and a profound nocturnal desaturation of oxyhemoglobin compared with the group without PA hypertension. Because hypoxia can enhance obesity-related inflammation,[30] it is most likely that the combined effects of profound night-time hypoxia and obesity-related inflammation have contributed to increases in PvR in patients with PA hypertension, leading to increases in PAD-PCWP gradient. Thus, hypoxic pulmonary vasoconstriction alone cannot explain the increased PAD-PCWP gradient in patients with PA hypertension in that study.

Limitations of the present study include the use of estimated pulmonary capillary pressure to derive PvR. PA pressure occlusion profile has been used previously to estimate pulmonary capillary pressure. However, a theoretical analysis of occlusion profile techniques has indicated that pulmonary capillary pressure is overestimated by the PA pressure occlusion profile and underestimated by the pulmonary venous occlusion profile.[31] In addition to the theoretical problems with PA pressure occlusion profile, some methodologic and technical problems may influence the interpretation of data.[32] Moreover, the increased PvR/TPVR ratios in patients with sepsis in the previous study,[7] in which the estimated pulmonary capillary pressure was used to derive PvR, were comparable with those in endotoxemic animals in another study[8] in which pulmonary capillary pressure was measured and were also comparable with those in patients with obesity in the present study. As such, our data based on the estimated PA output pressure are consistent with those in other studies. The reliability of using the estimated pulmonary capillary pressure to derive PvR and the possibility of measurement error have been described in detail previously.[7]

The presence of PAD-PCWP gradient makes the use of central venous pressure (right ventricular end-diastolic pressure) unreliable in assessing volume status in morbidly obese patients.

In addition, the supine posture promotes expiratory flow limitation and intrinsic positive end-expiratory pressure in obese patients.[33] The expiratory flow limitation and intrinsic positive end-expiratory pressure impair right ventricular filling.[34] This apparent right ventricular diastolic dysfunction is another factor that makes the use of central venous pressure reading unreliable in morbid obesity. Moreover, a previous study has shown that PA systolic storage (the fraction of right ventricular stroke volume stored in PA during systole and discharged into capillaries) decreases and the physiologic dead space–to–tidal volume ratio increases when PBV increases in morbidly obese patients with a high baseline PA systolic storage.‖ An increase in PA systolic storage has been shown to be associated with an improved distribution of ventilation-perfusion ratios in patients with acute respiratory distress syndrome.[14,35] Thus, it is likely that, depending on the baseline PBV, changes in PBV lead changes in the distribution of ventilation-perfusion ratios in obese patients in a different direction. As such, the management of adequate intravascular volume in patients with morbid obesity seems to be difficult without using PA catheter, particularly when they become critically ill, even though the use of PA catheter may not change the outcome of some critically ill patients.

An increase in PvR is not the only condition that is responsible for the increased PAD-PCWP gradient. Increased PAD-PCWP gradient contributed by increased PvR in morbid obesity could be interpreted erroneously as pulmonary embolism, because pulmonary embolism increases PAD-PCWP.[12,13] The measurement of PvR by using a PA catheter can be useful in determining whether the increased PAD-PCWP gradient is the result of increased PvR or increased PaR. Actually, the incidence of pulmonary embolism is higher in obese patients after bariatric surgery,[36] particularly in those with body mass index higher than 55 kg/m^2.[37] Because right ventricular dysfunction has been shown to have a prognostic value in patients with hemodynamically stable pulmonary embolism,[38] it is important to assess right ventricular function in this situation. Because of difficulties and limitations of echocardiography in the evaluation of right ventricular function in obese patients,[39] a PA catheter can be a handy tool. With a PA catheter in place, right ventricular function can easily be assessed by right ventricular systolic time intervals without requiring phonocardiography.[40] For bariatric surgery, particularly laparoscopic surgery, the use of PA catheter may not be necessary. However, if patients with morbid obesity become critically ill or require major surgery other than bariatric surgery, the use of PA catheter can be a valuable for perioperative management.

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The strong correlation between PAD-PCWP gradient and PvR/TPVR ratio in the present study suggests that an increase in PAD-PCWP gradient, which has been shown to be associated with high mortality in sepsis,[19] indicates the degree of low-grade inflammatory reaction in patients with morbid obesity. Patients with a higher PAD-PCWP gradient may have higher grade inflammatory reaction than those with a lower gradient. It will be interesting to find out whether weight reduction can reduce or eliminate PAD-PCWP gradient in these patients.

In summary, our data indicate that increased PvR contributes to increases in PAD-PCWP gradient in morbidly obese patients without daytime hypoxia. If the obesity-related inflammatory reaction is the pathophysiologic mechanism of increases in PvR, PAD-PCWP gradient could be an index of severity of the inflammatory reaction in morbidly obese patients without daytime hypoxia.

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

The Fourier representation of the pressure pulse can be written:

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

Because $M_n^2 = A_n^2 + B_n^2$, equation 1 can be rearranged as:

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

where PA(t) is PA pressure at time t, PA_0 is PA input pressure (mean PA pressure), M_n is modulus, Φ_n is the phase angle of harmonic form of recorded PA pressure at *n*th 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:

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

where Pa(t) is PA output pressure at time t, Pa_0 is mean PA output pressure, m_n is attenuated modulus, and $\{(\omega t + \Phi_n) - k \cdot \delta\}$ is the decreased angle of harmonic form of PA output pressure at nth harmonic. The transmission ratios are as follows: when the frequency is between 1 and 2, the ratio is 32.8%; between 3 and 4, 24.8%; between 4 and 5, 46.2%; and between 5 and 6, 25.6%.[15]

2. A decrease in the angle:

The decreased angle is as follows[41]:

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

where k is the rate of change of angle with distance δ (mean PA length). Because k 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,[42] the change of angle is as follows:

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

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.[16]

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

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

When t is zero and 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 $\{(\omega t - \Phi_n) - k \cdot \delta\}$, 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 PA output pressure curve to confirm that the pressure curve is not distorted, and to obtain the mean value.

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