Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: Incidence, clinical implications, and prognosis

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Context: **The incidence of acute cor pulmonale (ACP), a frequent and usually lethal complication of acute respiratory distress syndrome (ARDS) during traditional respiratory support, has never been re-evaluated since protective ventilation gained acceptance.**

Objective: **We performed a longitudinal transesophageal echocardiographic (TEE) study to determine whether this incidence, and its severe implications for prognosis, might have changed in our unit as we altered respiratory strategy.**

Design: **Prospective open clinical study.**

Setting: **Medical intensive care unit of a university hospital.**

Patients: **Seventy-five consecutive ARDS patients given respiratory support with airway pressure limitation (plateau pressure $\leq$30 cm H_2O).**

Interventions: **ACP was defined as a ratio of right ventricular end-diastolic area to left ventricular end-diastolic area in the long axis >0.6 associated with septal dyskinesia in the short axis during TEE examination.**

Results: **Normal right ventricular function was present in 56 patients, whereas right ventricular dysfunction was observed in 19 patients after 2 days of respiratory support. ACP was associated with pulmonary artery hypertension, increased heart rate, and decreased stroke index. Significant impairment of left ventricular diastolic function was also seen. All echo-Doppler abnormalities were reversible in patients who recovered, and the mortality rate was the same in both groups (32%). However, ACP patients who recovered required a longer period of respiratory support. A multivariate analysis individualized Paco2 level as the sole factor independently associated with ACP, suggesting that ACP development in ARDS is influenced by the severity of lung damage and/or the respiratory strategy.**

Conclusion: **Evaluation of right ventricular function by TEE in a group of 75 ARDS patients submitted to protective ventilation revealed the persistence of a 25% incidence of ACP, resulting in detrimental hemodynamic consequences associated with tachycardia. However, ACP was reversible in patients who recovered and did not increase mortality. (Crit Care Med 2001; 0:●●●–●●●)**

KEY WORDS: acute cor pulmonale; acute respiratory distress syndrome; circulatory failure; transesophageal echocardiography; protective ventilation

Based on an echocardiographic definition (1), massive pulmonary embolism and acute respiratory distress syndrome (ARDS) are the two main causes of acute cor pulmonale (ACP) in adults. ACP complicating massive pulmonary embolism has been found to be reversible in many studies, and this reversibility, leading to a high recovery rate with an adequate treatment, has been documented by two-dimensional echocardiography (2). Conversely, ACP complicating ARDS, which was also documented by two-dimensional echocardiography (3), was associated in the past with high mortality (3–6). This was consistent with previous anatomical studies showing that ARDS irreversibly damages the pulmonary microvasculature (7).

In recent years, protective ventilation, with airway pressure limitation, has led to major changes in respiratory support of ARDS patients. A recent clinical study performed in our unit demonstrated marked improvement in ARDS survival rate with this respiratory strategy (8). Thus, in the present prospective study, transesophageal echocardiography (TEE) was used to update the exact prevalence, clinical implications, and prognosis of ACP in an ARDS population submitted to protective ventilation.

PATIENTS AND METHODS

Patients. During a 5-yr period, from January 1996 to February 2001, among 934 patients free from prior cardiopulmonary disease and requiring emergency mechanical ventilation for an acute episode of respiratory failure, 75 met the ARDS criteria (9) on the first day of respiratory support and were enrolled in a longitudinal TEE study.

Monitoring and Severity Indexes. Hemodynamic monitoring included heart rate by an electrocardiographic lead, systemic arterial pressure by an indwelling radial artery catheter, central venous pressure, and continuous pulse oxymetry. Daily transthoracic echocardiography (TTE) was used to evaluate qualitatively both right and left ventricular function and to measure cardiac output by the Doppler technique (10). Additionally, the first TTE study performed at admission, which was also the first day of mechanical ventilation for each patient (day 1), permitted exclusion of any previously undiagnosed chronic cor pulmonale.

On the third day (day 3) of mechanical ventilation, we calculated the simplified acute physiology score (SAPS II) (11), logistic organ dysfunction score (LODS) (12), and lung injury severity score (LISS) (13).

Circulatory failure, defined as hypotension (systolic arterial pressure <90 mm Hg by invasive monitoring) despite apparently adequate fluid resuscitation (central venous pressure >12 mm Hg) and requiring continuous infusion of a vasoactive agent, was present in 59 cases at day 3. Vasoactive agents were used at the lowest dosage permitting a systolic ar-

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terial pressure >90 mm Hg by invasive monitoring. The amount of vasoactive agent used at day 3 was scored as follows: 1 for use of dopamine or dobutamine, regardless of the dosage; 2 for use of epinephrine or norepinephrine at a dosage <2 mg/hr; 3 for use of the same agents at a dosage between 2 and 5 mg/hr; and 4 for use of the same agents at a dosage >5 mg/hr.

The total fluid intake (including blood products, intravenously administered fluids, and enteral feedings) and output (including diuresis and fluid loss by hemodiafiltration) were carefully recorded, and permitted calculation of fluid balance (intake minus output) during the first 2 days of mechanical ventilation.

Respiratory Management. Mechanical ventilation (MV) was initiated in the controlled mode (Bennet 7200 respirator, Puritan-Bennett, Carlsbad, CA), limiting end-inspiratory plateau pressure to 30 cm H_2O, and included a tidal volume (TV) of 6–9 mL/kg and a respiratory rate of 12–16 cycles/min. Positive end-expiratory pressure (PEEP) was selected as improving oxygenation without requiring specific hemodynamic support, except for blood volume expansion. The result of this strategy was an average PEEP for the whole group of 7 ± 3 cm H_2O (range, 3–15 cm H_2O). To improve oxygenation without increasing PEEP, ventilation in the prone position was introduced at day 3 in 20 patients, because Pa_{O_2}/F_{IO_2} remained at <100 mm Hg. During MV in the controlled mode, patients were sedated with midazolam and sufentanyl, and sometimes paralyzed with venocuronium.

TEE. TEE was performed on each patient after 2 days of respiratory support (day 3) and was repeated once a week during an observational period of 4 wks. In our intensive care unit, right heart catheterization is never performed, and TEE is systematically used to assess the circulatory status of mechanically ventilated patients, giving more accurate images than TTE in this setting. This protocol was thus considered as a part of routine clinical practice and no informed consent was required from the patients' next of kin, as confirmed by the Clinical Research Ethics Committee of the French Intensive Care Society.

Echo-Doppler studies were performed with a Toshiba "Corevision" model SSA-350A (Toshiba, Otawara-Shi, Japan) equipped with a multiplane TEE transducer. Using the signal from the respirator, airway pressure was displayed on the screen of the echo-Doppler device, accurately timing cardiac events during the respiratory cycle, and permitting to average echo-Doppler measurements within the respiratory cycle.

Before introducing the TEE probe, TTE was performed by a subcostal approach to measure inferior vena caval diameter and to assess pulmonary artery systolic pressure (PAP_S), using the continuous-wave Doppler technique (14), with saline injection to enhance the signal from regurgitant flow when inadequate (15). The planimetry of the area of the color-coded regurgitant flow, when present, was performed on this view (16).

The multiplane TEE transducer was then positioned as follows:

1. To obtain the long-axis atrial plane, the transducer was positioned in the esophagus, the ultrasonic beam being perpendicular to the interatrial septum at the level of the fossa ovalis. From this plane, contrast echocardiography was used to detect a right-to-left shunt through a patent foramen ovale (17).
2. To obtain a four-chamber view of the cardiac cavities. From this view, left ventricular (LV) and right ventricular (RV) areas (A) were measured at end-diastole (ED) and at end-systole (ES). From these measurements, we calculated RV fractional area contraction (FAC) as (RVEDA−RVESA)/RVEDA, and RVEDA/LVEDA ratio. LVED and LVES long axes were measured as the distance from the apex to the midpoint of the mitral valve ring, and LV volumes (V) were calculated using the single-plane, area-length formula (18). Ejection fraction (EF) was calculated as (LVEDV−LVESV)/LVEDV. Peak velocity of the E wave and the A wave at the mitral level were also measured from this view by pulsed Doppler, and were expressed as E/A ratio (19). For this parameter, only the end-expiratory value was considered.
3. A short-axis, cross-sectional view of the LV at the mid-papillary muscle level was obtained by a transgastric approach. From these views, septal motion at end-systole/early diastole was carefully examined to detect any septal dyskinesia (SD). The latter was defined as a septal movement toward the left ventricular cavity center at the end-systole/onset of diastole, producing septal flattening or inverting septal curvature.
4. With the ultrasonic beam parallel to the long axis of the pulmonary artery, the Doppler sample volume was placed beyond the pulmonary valve in the mid-lumen of the pulmonary artery (PA), to record the PA flow. From pulsed Doppler spectrum recordings at a high speed of 5 cm/sec, we measured peak velocity (V_{max}), acceleration time (AcT), deceleration time (DcT), and flow period (FP). Mean acceleration (Ac_{mean}) was calculated as V_{max} /AcT.

The initial TEE at day 3 permitted separation of the patients into two groups, according to the absence (group 1) or presence (group 2) of ACP, which was defined as a dilated RV on the long-axis view (RVEDA/LVEDA >0.6) associated with SD on the short-axis view. Within group 2, we also individualized a subgroup of "severe" ACP, with a RVEDA/LVEDA ratio >1.

Statistical Analysis. Statistical calculations were performed using the Statgraphics plus package (Manugistics, Rockville, MD). Data are expressed as mean ± 1 SD. Between-group comparisons were performed using Student's *t*-test. A p value < .05 was considered as statistically significant. A least square linear regression analysis was also performed when appropriate.

We evaluated the predictive value for the probability of ACP, defined as an RVEDA/LVEDA ratio >0.6 associated with SD, of several baseline variables, including the patient's age, SAPS II, LODS, blood gas analysis (Pa_{O_2}/F_{IO_2}, Pa_{CO_2}), total compliance (CT), TV, plateau pressure, PEEP, and fluid balance at day 3. These variables were compared between the groups, and variables found to be significantly associated with RV dilation ($p \leq .20$) were entered into a logistic regression model, which allows simultaneous control of multiple factors. Adjusted odds ratio (OR) of ACP and 95% confidence interval (CI) were calculated for all independent significant predictors of ACP.

RESULTS

Patient Characteristics, Etiology of ARDS, and Incidence of ACP. The study population included 75 patients, 56 men and 19 women, with a mean age of 55 ± 16 yrs. Acute respiratory failure was caused by extensive bacterial pneumonia in 26 patients, aspiration pneumonia in 20 patients, septic shock of extrapulmonary origin complicated by acute lung injury in 25 patients, and miscellaneous causes in 4 cases. No significant between-group differences were observed in age, SAPS II, or LODS (Table 1). Average LISS was 2.6 ± 0.5, with a significantly higher value in group 2 (3 ± 0.3 vs. 2.5 ± 0.5 in group 1). Numbers of quadrants involved on chest radiograph was similar (3.3 ± 0.8 in group 1 vs. 3.5 ± 0.6 in group 2)

At the first TEE performed at day 3, 56 patients did not have ACP. These 56 patients constituted group 1, in which the average RVEDA/LVEDA ratio was 0.54 ± 0.12. On the same day, 19 patients exhibited ACP. These 19 patients constituted group 2, in which the average RVEDA/LVEDA ratio was 0.87 ± 0.23. Thus, the overall incidence of ACP was 25%. In group 2, four patients had a RVEDA/LVEDA ratio >1, and were individualized as "severe" ACP. Figure 1 shows a characteristic TEE pattern of ACP.

Pulmonary Circulation and RV Function. Echo-Doppler parameters of RV function are presented in Table 2. Significant between-group differences were noted: compared with group 1, group 2 was characterized by an elevated PAP_S, enlarged RV dimensions, and increased inferior vena caval diameter. No between-

Table 1. Individual predictors of acute cor pulmonale (ACP) Univariate analysis yielded all factors significantly associated with ACP (second column). Multivariate analysis including all these factors by logistic regression individualized factors independently associated with ACP (third column).

	Group 1	Group 2	Univariate *p*	Multivariate *p*	OR (CI)
Age, yrs	56 ± 16	52 ± 17	NS		
SAPS II	55 ± 17	49 ± 16	NS		
LODS	10.1 ± 4	9.9 ± 3.4	NS		
Pa_{O_2}/F_{IO_2}, mm Hg	115 ± 32	87 ± 24	.001	NS	
Pa_{CO_2}, mm Hg	47 ± 9	64 ± 12	.000003	.0001	1.15 (1.05–1.25)
CT, mL/cm H_2O	37 ± 11	31 ± 12	NS		
TV, mL/kg	8 ± 1	8 ± 1	NS		
Plateau, cm H_2O	23 ± 5	27 ± 4	.004	NS	
PEEP, cm H_2O	6 ± 3	9 ± 4	.0003	NS	
Fluid balance, mL	2300 ± 2400	3200 ± 2000	NS		

OR, odds ratio; CI, 95% confidence interval; SAPS, simplified acute physiology score; LODS, logistic organ dysfunction score; CT, total compliance; TV, tidal volume; PEEP, positive end-expiratory pressure.

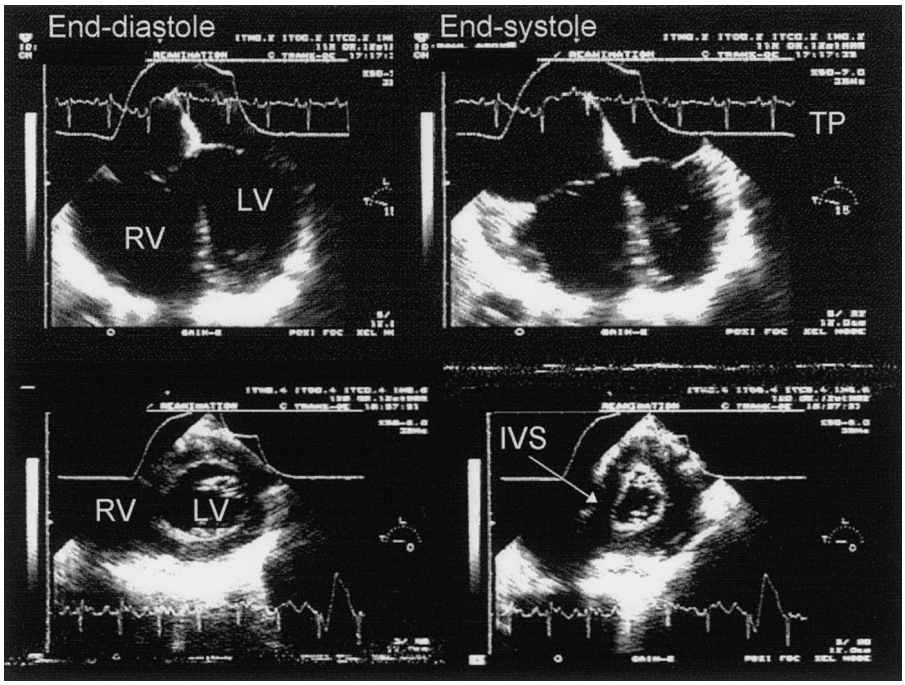

Figure 1. The characteristic echocardiographic patterns of acute cor pulmonale by transesophageal echocardiography. In the *upper panel*, right ventricular (*RV*) dilation is observed by a long-axis view, at end-diastole (*left*) and end-systole (*right*). Also note the reduced size of the left ventricle (*LV*). In the *lower panel*, septal dyskinesia is observed, in the same patient, by a short-axis view: at end-systole/early diastole (*right*) the interventricular septum (*IVS*) is shifted toward the LV cavity center, and the septal curvature is inverted (*arrow*). *TP*, tracheal pressure.

group difference was observed in RVFAC, which was not correlated with PAP_S ($r = .28, p = .37$). Between-group comparison did not reveal significant difference in pulmonary artery flow characteristics. A patent foramen ovale was evidenced in only one patient of group 1, and was never present in group 2 patients.

Systemic Hemodynamics and LV Function. General hemodynamic parameters and echo-Doppler parameters of LV function are presented in Table 3. Whereas no significant between-group differences were observed at day 3 in systolic arterial pressure or in cardiac index, group 2 patients had a significantly lower Doppler stroke index, despite a significantly increased central venous pressure, and exhibited a significant increase in heart rate. Compared with group 1, group 2 patients had a significantly reduced LVEDV, associated with an abnormal LV filling pattern with a predominant A wave. Characteristic reduction in LV dimensions is illustrated in Figure 1.

Table 2. Echo-Doppler evaluation of pulmonary artery hypertension and right ventricular function

	Group 1 (n = 56)	Group 2 (n = 19)
PAP_s, mm Hg	27 ± 9[a]	47 ± 8[b]
TR, cm^2	0.2 ± 0.5	2.2 ± 1.5[b]
IVC_{diam}, mm	17 ± 6	23 ± 5[b]
RVEDA, cm^2	8.5 ± 2.0	12.8 ± 3.6[b]
RVESA, cm^2	5.5 ± 1.9	8.9 ± 2.9[b]
RVFAC, %	36 ± 11	31 ± 11
V_{max}, m/sec	0.78 ± 0.20	0.82 ± 0.21
AcT, msec	91 ± 26	76 ± 27
DcT, msec	167 ± 50	168 ± 40
FP, msec	259 ± 52	244 ± 32
AC_{mean}, m/sec^2	9.6 ± 4.6	12.9 ± 6.4

PAP_s, pulmonary artery systolic pressure by continuous wave Doppler; TR, area of tricuspid regurgitation by color Doppler; IVC_{diam}, inferior vena caval diameter; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area contraction; V_{max}, peak velocity of pulmonary artery flow; AcT, acceleration time of the pulmonary artery flow; DcT, deceleration time of the pulmonary artery flow; FP, flow period (duration) of the pulmonary artery flow; AC_{mean}, mean acceleration of the pulmonary artery flow.

[a]An adequate measurement of PAP_s, which was easily obtained in the 19 patients of group 2, was only obtained in 22 patients of group 1; [b]$p < .05$.

Clinical Implications. The need for vasoactive agents at day 3, evaluated by our previously mentioned score, was similar in both groups (2.1 ± 1.5 and 2.6 ± 1.4 in groups 1 and 2, respectively). Also, no significant between-group differences were noted in fluid balance during the first 48 hrs of respiratory support.

Predictors of RV dilation are presented in Table 1. Among parameters significantly associated with ACP, only Pa_{CO_2} was a significant individual predictor of ACP.

As explained in the "Methods" section, ventilation in the prone position was introduced at day 3 in 20 patients (8 in group 1 and 12 in group 2) and markedly improved Pa_{O_2}/F_{IO_2}. This strategy, which was significantly more frequently used in group 2 (63% vs. 14% in group 1) permitted an immediate PEEP reduction in the patients concerned (from 12 ± 3 to 6 ± 2 cm H_2O).

Table 3. Systemic hemodynamic measurements and echo-Doppler evaluation of left ventricular function

	Group 1 (n = 56)	Group 2 (n = 19)
HR, beats/min	96 ± 19	112 ± 16[a]
SAP, mm Hg	114 ± 23	123 ± 25
CVP, mm Hg	12 ± 3	16 ± 3[a]
SI, cm^3/m^2	32 ± 9	25 ± 9[a]
CI, $L/min/m^2$	3.1 ± 0.9	2.7 ± 0.9
LVEDV, cm^3/m^2	60 ± 16	50 ± 15[a]
LVESV, cm^3/m^2	22 ± 10	24 ± 10
LVEF, %	53 ± 11	51 ± 16
E/A ratio, %	1.3 ± 0.4	0.8 ± 0.2[a]

HR, heart rate; SAP, systolic arterial pressure by invasive radial monitoring; CVP, central venous pressure; SI, stroke index by Doppler measurement at the level of the left ventricular outflow tract; CI, cardiac index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; E/A ratio, ratio of respective early (E) and late (A) peak velocities at the mitral level.

[a] $p < .05$.

Prognosis Implications of ACP. The average mortality rate for the whole group was 32%. This mortality rate seemed not to be influenced by the presence of ACP, because both groups also had a 32% mortality rate. The subgroup of patients with "severe" ACP (four cases in whom RVEDA/LVEDA ratio was >1) had a mortality rate of 25%.

The average duration of mechanical ventilation for the whole group was 16 ± 11 days, with a nonsignificant between-group difference (15 ± 10 and 20 ± 16 days in groups 1 and 2, respectively). However, the number of days of unassisted ventilation during the observational period of 28 days was significantly larger in group 1 (9 ± 9 vs. 4 ± 5 in group 2). Accordingly, patients in group 2 who recovered required a longer duration of mechanical ventilation.

The evolution of ACP during the longitudinal TEE study is illustrated in Figure 2. Echocardiographic abnormalities progressively disappeared in patients who recovered.

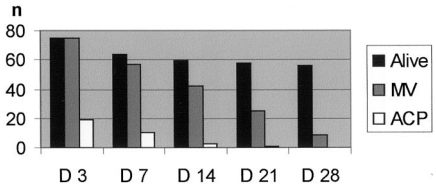

Figure 2. Change in acute cor pulmonale (*ACP*) incidence during the longitudinal study. The number (*n*) of patients is shown on the y-axis. The observational period is shown on the x-axis, which each group of columns representing a transesophageal echocardiography (TEE) evaluation. *Alive*, number of patients still alive; *MV*, number of patients still on mechanical ventilation, the difference between these two columns being the number of patients definitively weaned from respiratory support; *ACP*, number of patients still presenting ACP on TEE; *D*, day.

DISCUSSION

Pulmonary hypertension in ARDS was first described in 1977 by Zapol and Snider (20), who focused on the abnormal increase in pulmonary vascular resistance observed in this syndrome, and demonstrated a consequent increase in RV stroke work index. LV impairment was also noted (20), and progressive RV dilation was advocated to explain the progressive and refractory circulatory failure observed in these patients after several days on respiratory support (21). Other studies have confirmed these findings (3–6, 22). In particular, RV dilation was illustrated by radionuclide angiography (23) and by two-dimensional echocardiography (3). Before 1990, pulmonary artery hypertension and RV dilation observed in ARDS were associated with a poor prognosis (3–6), and progressive and irreversible obstruction of pulmonary microcirculation was considered a hallmark of the syndrome (4).

We have previously described the echocardiographic patterns of ACP and defined RV dilation as an RVEDA/LVEDA ratio >0.6 in a long-axis view (1). However, a moderate RV dilation does not necessarily denote RV dysfunction. But when RV dilation is associated with septal dyskinesia, it reflects the presence of right ventricular pressure overload (24–26). In this group of 75 ARDS patients submitted to protective ventilation, we found by TEE an ACP prevalence of 25%, with a progressive return to a normal echocardiographic pattern over days or weeks when patients recovered from ARDS. This study also emphasized the clinical implication of the presence of ACP in ARDS. By impairing LV diastolic filling, RV dysfunction significantly reduced LV stroke output, and cardiac output was maintained by marked tachycardia in these patients.

A fundamental question raised by this study is the respective responsibility of ARDS per se, and of respiratory support, in determining ACP in this setting. The only independent factor related to ACP in the present study was $Paco_2$, a parameter influenced by the severity of lung damage. However, this factor is also influenced by the respiratory strategy limiting TV. One may also wonder about the relative impact on ACP recovery of the spontaneous course of the syndrome and the respiratory strategy. Our present data do not provide any definitive answer. Tracheal intubation was decided in emergencies and it was usually not possible to explore RV by TEE before mechanical ventilation. And because we have long considered PEEP as an afterloading factor for RV (27), ventilation in the prone position has been systematically initiated at day 3 when Pao_2/Fio_2 remained <100 mm Hg, allowing PEEP to be reduced. But this strategy, guided by the imperative of limiting RV load, precluded any conclusion regarding its exact impact on ACP recovery. It should, however, be noted that we had to use this strategy more often when ACP was present.

Historic studies using right heart catheterization have associated pulmonary hypertension in ARDS with a poor prognosis (3–6). Right heart catheterization, which accurately measures pulmonary artery pressure, cannot detect ACP with the same accuracy as echocardiography because the level of pulmonary hypertension producing RV afterloading may vary from patient to patient. In 1985, we used a transthoracic approach in the only echocardiographic study in ARDS

We have observed a prevalence of acute cor pulmonale of 25% during transesophageal echocardiography performed during respiratory support in a group of 75 acute respiratory distress syndrome patients undergoing mechanical ventilation with airway pressure limitation.

submitted to a conventional respiratory support without airway pressure limitation (3). In this historic study, we observed a 61% prevalence of ACP, and a clear impact of this complication on mortality rate (57% vs. 33% in patients free from ACP) (3). Tidal ventilation often results in interposition of the lung between the heart and probe, and we now prefer the transesophageal approach, which permits a perfect RV examination throughout the respiratory cycle. The present study suggests that the frequency of ACP in ARDS might have declined. In our opinion, this decline might be explained in part by fundamental alterations in respiratory support. Normocapnic ventilation was our guiding principle 15–20 yrs ago, and was obtained with high TVs (>12 mL/kg) (8). In a recent clinical study, we have clearly individualized TV as a significant afterloading factor for the RV (28), and protective ventilation is currently used in our unit. However, the present study also suggested some limits to this strategy, because the degree of hypercapnia was significantly associated with ACP. Experimentally, hypercapnia impairs performance of an afterloaded RV (29).

In conclusion, we have observed a prevalence of ACP of 25% during TEE performed during respiratory support in a group of 75 ARDS patients undergoing mechanical ventilation with airway pressure limitation. This potentially reversible complication of acute pulmonary hypertension necessitated a longer period of assisted ventilation before recovery and, with our respiratory strategy, a more frequent use of prone positioning. With these requirements, however, ACP did not have a negative influence of final recovery in the present cohort.

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