Circulatory Effects of Weaning from Mechanical Ventilation: The Importance of Transdiaphragmatic Pressure

WHAT IS THE MAJOR difference between the effect of spontaneous ventilation and that of intermittent positive-pressure ventilation on the circulatory system? During spontaneous ventilation, the airway pressure remains relatively constant, but, during conventional mechanical ventilation, the airway pressure rises. In pulmonary edema from acute left ventricular failure, our intuition tells us that positive pressure in the airways should be beneficial. There is a notable history of the use of continuous positive-pressure ventilation in the treatment of pulmonary edema from left ventricular failure beginning with the work of Emerson early in this century[1] and later popularized by Barach.[2] The mechanism proposed by Emerson and by Barach to account for its effectiveness was that positive airway pressure pushed fluid from the lungs back into the blood. When I ask a nurse, resident, or medical student why a patient with left ventricular failure often does better receiving positive-pressure ventilation, the answer I am most likely to get is along the lines proposed by Emerson and by Barach. Ironically, the major circulatory differences between spontaneous and mechanical ventilation have little to do with the difference in airway pressure and nearly everything to do with the difference in pleural and abdominal pressure.

When the respiratory muscles take over the work provided by the mechanical ventilator, the airway pressure relative to pleural pressure, the transpulmonary pressure, is unaltered because transpulmonary pressure depends only on the mechanical properties of the lungs. While it is true that mean airway and pleural pressure are lower during spontaneous than during intermittant positive-pressure ventilation, they are not changed relative to each other. As long as transpulmonary pressure remains unaltered, there is no direct effect on the heart or pulmonary vessels. When I travel from Baltimore to Denver, both my airway and my pleural pressure decrease by approximately 130 mmHg, a change orders of magnitude greater than the changes that occur between mechanical and spontaneous ventilation, but my lungs are not congested and there is no added impediment to the ejection of blood from my left ventricle. The reason there is no change is that there is an equal decrease in the pressure around my systemic vessels. If I took my thorax and its contents to Denver and left the rest of my body in Baltimore (assuming low resistance and noncompliant conduits!), nearly all the blood would be pushed into the heart and pulmonary vessels, and my left ventricle could hardly eject any blood. In addition, my diaphragm could not generate enough tension to descend because of the high abdominal pressure relative to thoracic pressure. The high pressure surrounding the systemic blood vessels relative to the pressure around the right ventricle causes an increase in preload of the right heart, and the high pressure around the systemic vessels relative to the pressure around the left heart causes an increase in afterload of the left heart.

In the paper of Lemaire et al. in this issue of ANESTHESIOLOGY,[3] patients with left ventricular dysfunction weaned from mechanical ventilation reduced the pressure around their heart and lungs by an average of 7 mmHg. The authors feel that it was this decrease in pressure that produced acute left ventricular failure through an increase in preload and afterload. It is refreshing to see that they emphasize changes in pleural pressure and not the more apparent changes in airway pressure. Indeed, the changes in pleural pressure are not at all apparent, and the authors had to quantify these changes by the special technique of measurement of esophageal pressure.

Lemaire et al. present compelling evidence that left ventricular failure occurred during spontaneous ventilation, and the measurements of heart volumes and vascular pressures strongly suggest that there was an increase in both preload and afterload when mechanical ventilation was terminated. If, indeed, the changes in preload and afterload produced by such small changes in pleural pressure were the cause of the acute left ventricular failure, this work emphasizes the great importance of ventilatory mechanics in the setting of compromised heart function. Further, if such small changes in one direction can produce failure, small changes in the opposite direction can be used for therapy.[4]

Is a change in pressure around the heart of a few mmHg sufficient to cause the large change in preload and afterload? There has been considerable controversy concerning the magnitude of the effect of pleural pressure on afterload, but general acceptance of a major

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effect on preload. We know from Guyton's work that a small change in the right atrial pressure can have a large effect on venous return because the gradient of venous return is so small.[5] If the only effect on preload were from the decrease in the pressure around the right heart, there could be no increase in the gradient of venous return without a decrease in right atrial pressure relative to atmospheric pressure. From the data of table 2 in the paper of Lemaire et al., surprisingly, it appears that the right atrial pressure rose relative to atmospheric pressure, for the right atrial transmural pressure rose more than the pleural pressure fell. This was so unexpected that I contacted one of the authors (Zapol) about this question. He said that this often happened, and he sent me a recorder tracing from one of the patients showing a large rise in right atrial pressure relative to atmospheric pressure during spontaneous ventilation, i.e., the same pattern as the pulmonary artery occlusion pressure shown in Lemaire et al.'s figure 1. How, then, could the decrease in plural pressure be responsible for the increase in preload? It cannot be; therefore, something else must be going on, and I believe the paradox can be resolved by a consideration of abdominal pressure.

During mechanical ventilation, the diaphragm is relaxed. During spontaneous ventilation, the muscles of the diaphragm contract, and this requires an increase in active tension. It is this increase in the active tension of the diaphragm that is responsible, in part, for the fall in pleural pressure. The magnitude of the increase in active diaphragmatic tension is only partly reflected by the fall in pleural pressure, but is more directly a function of the difference between pleural and abdominal pressure, the transdiaphragmatic pressure. During mechanical ventilation with the diaphragm relaxed, the rise in pleural pressure during inspiration is accompanied by a parallel increase in abdominal pressure with little change in transdiaphragmatic pressure. During spontaneous inspiration, the descent of the diaphragm produces a fall in pleural pressure and an increase in abdominal pressure.

We do not know the values of abdominal pressure in the patients of Lemaire et al., but it is likely that the pressure in the stomach (as an indicator of abdominal pressure) changed in parallel with esophageal pressure during mechanical ventilation, but rose at the same time that esophageal pressure fell during spontaneous breathing.

The splanchnic circulation has a much greater compliance and resistance to venous return than the rest of the systemic circulation.[6] These special mechanical properties allow the splanchnic circulation to play a profoundly important role in the regulation of venous return through changes in its arteriolar and venous tone.[7] In essence, the splanchnic circulation acts as a functional reservoir to adjust venous return and preload during various types of physiological stress, such as exercise and changes in posture and environmental temperature. The mechanical properties of the splanchnic blood vessels make them especially sensitive to changes in the pressure on their outer surface.[8] A small increase in abdominal pressure is capable of causing a marked increase in preload, and this becomes exaggerated when the systemic circulation is congested, as in conditions where hepatajugular reflux is present.

On the basis of these considerations, it is more likely that the major cause of the increase in preload in going from mechanical to spontaneous ventilation was the increase in transdiaphragmatic pressure rather than the fall in pleural pressure. The strongest support for the importance of transdiaphragmatic rather than pleural pressure comes from the comparison of the two episodes of mechanical weaning. During the second episode, the fall in pleural pressure was even greater, but it seems likely that the increase in transdiaphragmatic pressure was considerably less. There is little reason to believe that 1 week of diuretic therapy had a significant effect on myocardial contractility, but the significant decrease in weight of 5 kg and blood volume of 1 kg between the first and second episodes could have resulted in a much smaller translocation of blood from the systemic circulation to the heart and lungs if we consider the role of transdiaphragmatic pressure.

It is highly likely that a large portion of the 5-kg weight decrease came from a loss of edema and blood volume from the abdominal viscera. Slight adjustments in vascular tone could maintain preload constant during the slow loss of blood volume in the week of diuretics. These are the expected physiological adaptations to loss of blood volume, and it is not surprising that there were not significant differences in the circulatory measurements while the patients were receiving mechanical ventilation. A decrease in abdominal volume during the week of diuretics could have had a huge effect on abdominal compliance, such that, with descent of the diaphragm during the second episode of spontaneous inspiration, the abdominal pressure rose considerably less than during the first. Compatible with the smaller increase in abdominal pressure during the second episode is the reversal of the direction of the change in right atrial pressure relative to atmospheric pressure. The transmural right atrial pressure now rose less than the esophageal pressure fell (from analysis of data received from Dr. Zapol).

While no measurements of abdominal pressure were made, further analysis of the data from Dr. Zapol lends support to the concept that when a patient is weaned from mechanical ventilation: 1) the major circulatory

changes are due to both an increase in preload and afterload, and 2) the increase in preload and afterload are largely the result of an increase in transdiaphragmatic pressure rather than a decrease in pleural pressure. These conclusions are based on the following considerations.

If the increase in transdiaphragmatic pressure caused an increase in both preload and afterload, we would expect a significant increase in both right atrial transmural pressure and decrease in left ventricular ejection fraction in going from mechanical to spontaneous ventilation. Furthermore, if the major difference in the circulatory response between the two episodes were due to the difference in abdominal pressure, we would expect to find a smaller increase in right atrial transmural pressure and a smaller decrease in left ventricular ejection fraction per mmHg fall in esophageal pressure between the first and second episodes. From the data I received from Dr. Zapol, these expectations are met. The right atrial transmural pressure increased 1.6 mmHg per 1 mmHg decrease in esophageal pressure during the first episode, and only 0.8 mmHg/mmHg during the second ($P < .05$ by paired t analysis). (Note that the ratio was greater than 1 on the first episode and less than 1 on the second, related to the directional change in right atrial pressure relative to atmospheric pressure.) The decrease in left ventricular ejection fraction in relation to the decrease in esophageal pressure was 2.3%/mmHg and -0.1%/mmHg ($P < .05$ by paired t analysis) between the first and second episodes, respectively.

Because the transdiaphragmatic pressure is directly related to the muscular tension of the diaphragm, it is a major determinant of the energy requirements of the diaphragm. Furthermore, there is evidence that diaphragmatic tension impedes diaphragmatic blood flow through mechanical compression of the muscular blood vessels. The magnitude of the transdiaphragmatic pressure is probably the single most important factor in the relation between supply and demand of energy, and, thus, plays a major role in determining whether respiratory muscle fatigue will or will not be present.[9]

If the abdominal viscera are congested and the compliance of the abdominal cavity reduced, the transdiaphragmatic pressure will have to increase more to provide the same tidal volume during spontaneous breathing. The magnitude of the decrease in pleural pressure during spontaneous inspiration for a given tidal volume is proportional to the elastic and resistive properties of the lungs. With no change in the mechanical properties of the lungs, the greater the rise in abdominal pressure, the greater the energy requirements and the less the diaphragmatic blood flow (unless adjusted through autoregulation). If we now add to these factors an increase

in preload and afterload in the presence of compromised heart function, the burden on the diaphragm becomes even greater; for it is not unlikely that the pulmonary congestion causes the lungs to be stiffer, and the transdiaphragmatic pressure will have to be even greater to provide the same tidal volume. It is not difficult to see how this vicious circle will lead to diaphragmatic fatigue and inability to sustain spontaneous ventilation.

I believe that just such a vicious circle was occurring in the patients studied by Lemaire et al. during the first attempt at weaning. If the study had not been repeated after a short time of diuretic therapy, the significance of that vicious circle could have been suspected, but would have been only one theoretical factor among a multitude of others that could be responsible for why a patient could not be weaned. Even the convincing demonstration of the development of left ventricular failure on the first attempt at weaning could have been interpreted as the result of the inability of the patients to maintain adequate ventilation. It is not unreasonable that the rise in P_{CO_2} and increase in oxygen consumption could have been the cause of the failure. The authors state that they "cannot dissociate cause from effect."

In my opinion, the major contribution of the study of Lemaire et al. is that they repeated it after diuresis. The importance of the repetition is not that the patients could now be weaned or that left ventricular failure did not occur. This could have been related to improvement from factors other than diuresis. From my point of view, the great contribution is that the data can be used to test our speculations on why left ventricular failure occurred on the first weaning attempt and not the second. I am completely unable to explain the differences without invoking the role of transdiaphragmatic pressure to account for the major circulatory and respiratory changes between mechanical and spontaneous ventilation in patients with compromised heart function. But once I am forced to think about transdiaphragmatic pressure, I now see a most attractive picture clearly for the first time, and this picture gives me new insight into the complicated and important interactions between circulation and respiration.

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Acute Left Ventricular Dysfunction during Unsuccessful Weaning from Mechanical Ventilation

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The authors studied the hemodynamic effects of rapidly weaning from mechanical ventilation (MV) 15 patients with severe chronic obstructive pulmonary disease (COPD) and cardiovascular disease who were recovering from acute cardiopulmonary decompensation. In each patient, 10 min of spontaneous ventilation (SV) with supplemental oxygen resulted in reducing the mean esophageal pressure ($\bar{X} \pm$ SD, $+ 5 \pm 3$ to -2 ± 2.5 mmHg, $P < .01$) and increasing cardiac index (CI) 3.2 ± 0.9 to 4.3 ± 1.3 l/min/M², $P < .001$), systemic blood pressure (BP 77 ± 12 to 90 ± 11 mmHg, $P < .001$), heart rate (HR 97 ± 12 to 112 ± 16 beats/min, $P < .001$), and, most importantly, transmural pulmonary artery occlusion pressure markedly increased (PAOP$_{tm}$ 8 ± 5 to 25 ± 13 mmHg, $P < .001$), mandating a reinstitution of MV. In four patients with left ventricular (LV) catheters, the PAOP correlated with the LV end-diastolic pressure during both MV and SV. Gated blood pool imaging showed SV increased the LV end-diastolic volume index (65 ± 24 to 83 ± 32/M², $P < .002$) with LV ejection fraction unchanged. Patients were treated for a mean of 10 days with diuretics, resulting in a reduction of blood volume (4.55 ± 0.9 l to 3.56 ± 0.55 l) and body weight (-5 kg, $P < .001$). Subsequently, nine of the 15 patients were weaned successfully from mechanical ventilation with unchanged PAOP. (Key words: Chronic obstructive pulmonary disease. Heart: failure. Lung: respiratory failure. Ventilation, mechanical: weaning.)

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WHEN PATIENTS WITH chronic obstructive pulmonary disease (COPD) and diminished respiratory reserve are recovering from acute exacerbations of respiratory failure, they can become completely dependent on me-

chanical ventilatory support, spending weeks or even months receiving ventilatory care. Disconnected from the ventilator, these patients can rapidly develop ineffective low tidal volume respiration, tachypnea, evidence of sympathetic nervous system hyperactivity (tachycardia, systemic hypertension, sweating), and, if spontaneous ventilation (SV) persists for several minutes, hypercapnea and hypoxia.[1] Such ventilatory decompensation can be induced either by discontinuing mechanical ventilation (MV) or by rapidly reducing mechanical ventilator rates during intermittent mandatory ventilation.[2]

During these episodes of acute ventilatory decompensation, we noted the frequent occurrence of wheezing, suggesting cardiac asthma or bronchospasm. Since many of our patients with COPD had a history of myocardial infarction and angina, as well as electrocardiogram (ECG) evidence of coronary artery disease, we suspected that acute left ventricular dysfunction might be an important impediment to weaning. Referring to studies of the interaction between the ventilatory and circulatory systems that demonstrate that reducing the intrathoracic pressures during SV can increase both left ventricular preload[3] and afterload,[4,5] we hypothesized that, in patients with previously impaired cardiac function, the hemodynamic stress produced by SV could cause acute LV dysfunction. Measurements of PAOP that would document LV failure during SV have not been reported in these patients, perhaps because, usually, they are discharged from the ICU and committed to long-term ventilation in intermediary care units.

To search for evidence of LV failure, we prospectively examined a group of patients who had resolved their acute phase of lung disease and who were difficult to wean from MV. Their inspiratory force, vital capacity, minute ventilation, and tidal volume appeared sufficient to permit sustained spontaneous ventilation[1,6,7]; however, none of these patients could be weaned from the ventilator. Therefore, radial and pulmonary artery catheters were inserted and gated blood pool scintiscanning was performed to examine their cardiopulmonary performance during MV and SV.

Materials and Methods

Fifteen adult patients were studied in the medical Intensive Care Unit of Henri Mondor Hospital. The pa-

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TABLE 1. Clinical Description of COPD Patients with Outcome

Patient	Age	Sex	Prior Cardiocirculatory Disease	Cause of ARF	Duration of MV Before Study (Weeks)	Ventilatory Outcome W/D	Hospital Survival/ Death
1	64	F	Systemic hypertension*	Bacterial pneumonia	12	D	Death
2	66	M	Systemic hypertension, myocardial ischemia	Post op vascular surgery	2	D	Death
3	64	F	Cor pulmonale	Acute bronchitis	1	W	Survival
4	75	M	Cardiomyopathy*	Bacterial pneumonia	6	D	Death
5	74	M	Cor pulmonale	Bacterial pneumonia	2	W	Survival
6	71	F	Myocardial infarction*	Post-op vascular surgery	2	D	Death
7	54	M	Cor pulmonale	Bacterial penumonia	4	W	Survival
8	73	M	Cor pulmonale	Bacterial pneumonia	4	D	Survival
9	64	M	Myocardial infarction, Cor pulmonale	Bacterial pneumonia	8	W	Survival
10	76	M	Systemic hypertension	Acute bronchitis	1	W	Survival
11	42	M	Cardiomyopathy	Acute bronchitis	1	W	Survival
12	64	M	Myocardial infarction, Cor pulmonale	Acute bronchitis	6	W	Survival
13	69	M	Cardiomyopathy Systemic hypertension	Ileus	4	W	Survival
14	72	M	Myocardial infarction	Post-op abdominal surgery	3	D	Death
15	60	F	Cor pulmonale Cardiomyopathy	Acute bronchitis	2	W	Survival

D-remained dependent upon mechanical ventilation; W = weaned from mechanical ventilation; ARF = acute respiratory failure; MV = mechanical ventilation.

* Autopsy demonstrated severe diffuse coronary atherosclerotic occlusions.

tients, their diagnoses, and other clinical information are listed in table 1. All patients had severe COPD and acute ventilatory decompensation requiring MV. Eleven suffered an acute bout of pulmonary inflammation involving increased secretion of purulent sputum, and six of these had radiographic evidence of lung consolidation. Three additional patients had acute ventilatory insufficiency following abdominal surgery and one after an ileus. The criteria for selecting patients for study were: acute exacerbation of lung disease had been resolved for several days to weeks, either the trachea had remained intubated or tracheostomy was present; the patient was receiving mechanical ventilation despite the fact that ventilatory capacities exceeded standard criteria for successful weaning[6,7]; and the patient did not tolerate weaning from the ventilator for over 30 min on at least two trials.

In these 15 patients weighing 60 ± 11 kg ($\bar{X} \pm SD$), mean spontaneous tidal volume after 10 min of SV was 311 ± 44 ml, mean vital capacity was 986 ± 216 ml, mean inspiratory force was -30 ± 9 cm H_2O, mean minute ventilation was 7.7 ± 1.7 l/min, and mean ventilatory rate was 25 ± 7/min. Although there are no uniformly accepted or standard criteria for weaning patients, these values lie within satisfactory ranges for successful weaning. Eight of 15 patients received bronchodilator therapy.

A diagnosis of COPD was reached after clinical investigation revealed a history of chronic bronchitis and/or emphysema, and radiographic and pulmonary function tests showed abnormalities characteristic of severe airway obstruction. Ten of the patients had pulmonary function tests in the months prior to admission, their average vital capacity was $51 \pm 17\%$ predicted, FEV_1 $28.8 \pm 6.4\%$ predicted, and the Pa_{CO_2} of seven was 39.6 ± 4 mmHg.

Arterial blood pressure was monitored continuously with a radial artery catheter and transducer system. A balloon flotation pulmonary artery catheter was inserted *via* an internal jugular vein to measure pulmonary artery pressure and pulmonary artery occlusion pressure (PAOP) at end expiration. Cardiac output, determined with an Edwards Model 9250A computer, was the mean of three measurements obtained by injecting 10 ml of a 0° C dextrose solution. In four patients (patients 1, 3, 5, and 8), a sterile 7 F pigtail catheter was inserted percutaneously, using the Seldinger technique, *via* a common femoral artery into the left ventricle. In these patients, we compared the PAOP with the simultaneously measured LVEDP. A fluid-filled 4 mm diameter silicone catheter was used to measure esophageal pressure (Peso)[8] that was planimetered to obtain the mean value. To calculate end-expiratory transmural PAOP, we subtracted the instantaneous end-expiratory values of PAOP and Peso. Patients were supine during all pressure measurement and isotope studies.

ISOTOPES

Blood volume was estimated by injecting and, later, sampling autologous red blood cells labeled with ^{51}Cr.[9] Values reported are % predicted. Cardiac scintigraphy was carried out by *in vivo* red cell labelling using stannous pyrophosphate with 555–815 MBq of ^{99}Tc. Car-

diac output, measured using the Stewart-Hamilton principle during the first pass of the tracer,[10] was only used to calculate stroke volume index (SVI) (cardiac index/heart rate) and ventricular volumes. All the other values in tables 2 and 3 were determined using thermodilution cardiac outputs. In four patients in whom both measurements were performed, there was no difference between thermal dilution cardiac index and nuclear determinations of cardiac index. Then, ECG-gated radionuclide angiography was performed using an equilibrium blood pool technique with a gamma camera (Model CGR Acticamera®, BAC, France; with a Simis 3 Computer) in the LAO projection optimized for ventricular separation. Right and left ventricular ejection fractions were computed by standard techniques[11]; end-diastolic volume index (EDVI) was calculated as EDVI = SVI/EF.

PROTOCOL

Fifteen patients who repeatedly failed to wean from MV were identified. Informed consent was obtained from the patients and the study was approved by the Ethics Commitee of the "Societe de Reanimation de Langue Francaise." Catheters were inserted and all patients underwent controlled MV with a Siemens 900C ventilator with FI_{O_2} 0.3–0.6 at a rate of 12–18 breaths/min, and tidal volume of 6–10 ml/kg without positive end-expiratory pressure (PEEP). When a stable hemodynamic state was obtained, pulmonary and systemic hemodynamic measurements and blood gas tensions were recorded (table 2, MV). Then the patient, still connected to the Siemens 900C, was allowed to spontaneously ventilate without PEEP. After 10 min, pulmonary and systemic hemodynamic values were recorded and arterial and mixed venous blood samples were obtained. If an LV catheter had been inserted, LVEDP was measured before and after 10 min of SV_1. The patient was again mechanically ventilated, and 12 of the patients were transported to the nuclear medicine department, as French government regulations prevent the use of radioisotopes outside nuclear medical facilities. Red blood cells labelled with ^{51}Cr and ^{99m}Tc were injected. Thus, approximately 30 min after a SV hemodynamic study was completed in the intensive care unit, the heart was imaged for 10 min while the patient was being mechanically ventilated. CI, RVEF and LVEF, and end-diastolic volumes were computed. Then, a period of SV was begun again in the nuclear medicine facility, scintigraphic data collected for 10 min, and the patient returned to MV and transferred to the intensive care unit. Measures of hemodynamic events recorded on strip charts in the intensive care unit and monitored on an oscillograph in the nuclear medicine facility did not differ between these two sequential weaning epi-

TABLE 2. Hemodynamic Scintigraphic and Gas Exchange Values during Continuous Mechanical Ventilation (MV) and after 10 Min of Spontaneous Ventilation (SV_1)

	Peso	CI	HR	SVI	PAOP tm	PAP tm	RAP tm	BP	LVEDVI	LVEF	RVEDVI	RVEF	PaO₂	PaCO₂	VO₂
MV	+5 ± 3	3.2 ± 0.9	97 ± 12	34 ± 11	7.5 ± 5	24 ± 6	3 ± 5	77 ± 12	65 ± 24	54 ± 15	83 ± 33	30 ± 8	103 ± 28	42 ± 6	165 ± 41
SV	-2 ± 2.5	4.3 ± 1.3	112 ± 16	40 ± 14	24.5 ± 13	40 ± 14	15 ± 5.5	90 ± 11	83 ± 32	49 ± 13	103 ± 39	27 ± 8	74 ± 25	58 ± 10	182 ± 55
n	15	15	15	15	15	15	15	15	12	12	10	10	15	15	15
t	7.34	5.83	5.02	3.12	6.03	5.69	7.70	5.01	4.03	3.04	5.36	1.65	6.50	8.02	3.21
P	*	*	*	*	*	*	*	*	*	NS	*		*	*	*

Peso = esophageal pressure (mmHg); CI = cardiac index (l/min/m²); HR = heart rate (b/min); SVI = stroke volume index (ml/m²); PAOP = end-expiratory transmural pulmonary artery occluded pressure (mmHg); PAP = mean pulmonary artery pressure (mmHg); BP = blood pressure (mmHg); RAP = transmural right atrial pressure (mmHg); LVEDVI = left ventricular end diastolic volume index (ml/m²); LVEF = left ventricular ejection fraction (%); RVEDVI = right ventricular end diastolic volume index (ml/m²); RVEF = right ventricular ejection fraction (%); PaO₂ = arterial oxygen tension (mmHg); PaCO₂ = arterial carbon dioxide tension (mmHg); VO₂ = oxygen uptake (ml O₂/min/m²).
* Significant at the 0.05 level.

TABLE 3. A Comparison of Hemodynamics, Gas Tensions, and Other Measurements in Patients Studied at Both SV_1 and SV_2

| | Weight | Blood Volume | | Peso | CI | PAOP (tm) | PAP (tm) | BP | LVEDVI | RVEDVI | Pa_{O_2} | Pa_{CO_2} |
		kg	% Predicted									
SV_1	60 ± 11	4.55 ± 0.9	123 ± 22	−1.9 ± 2.6	4.3 ± 1.0	25 ± 15	40 ± 13	87 ± 10	89 ± 28	122 ± 37	77 ± 25	57 ± 10
SV_2	55 ± 10	3.56 ± 0.55	102 ± 19	−3.8 ± 1.4	3.77 ± 0.7	9 ± 3	27 ± 8	88 ± 15	65 ± 20	103 ± 41	83 ± 26	50 ± 6
n	12	8	8	8	8	8	8	8	8	5	12	8
t	6.49	2.87	2.33		1.24	3.67	2.55	0.21	2.47	1.16	0.012	2.23
P	*	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS

Peso = esophageal pressure (mmHg); CI = cardiac index (l/min/m²); PAOP = transmural end-expiratory pulmonary artery excluded pressure (mmHg); PAP = mean transmural pulmonary artery pressure (mmHg); BP = blood pressure (mmHg); LVEDVI = left ventricular end-diastolic volume index (ml/m²); RVEDVI = right ventricular end-diastolic volume index (ml/m²); Pa_{O_2} = arterial oxygen tension (mmHg); Pa_{CO_2} = arterial carbon dioxide tension (mmHg); NS = not significant. * Significant at the simultaneous 0.05 level.

sodes; values from the strip-chart recordings are reported in this manuscript.

Patients were then treated with controlled mechanical ventilation supplemented by intravenous furosemide (80 mg/day). They received feedings of 2000 kcal per day, orally or *via* a naso-gastric tube. Nine patients eventually weaned from MV to SV and were discharged; about 1 week after the first study, eight of these underwent repeat radial and pulmonary artery catheterization and scintigraphic and blood volume studies after weaning (SV_2). One patient (patient 8) was discharged from the hospital requiring mechanical ventilation and died 5 months later. Five patients died from heart failure, pneumonia, and infection while still in the hospital; autopsies were performed on three, and each demonstrated extensive coronary atherosclerosis (table 1).

CATECHOLAMINES

Blood samples were obtained from eight patients for analysis of the levels of epinephrine and norepinephrine before and 10 min after weaning (SV_1). Catecholamines were measured by the enzymatic methods of Brown and Jenner.[12] In our laboratory, the coefficients of variation of the measurements were 3.1% for norepinephrine and 3.3% for epinephrine. Sensitivity was 1.5 pg/ml for both norepinephrine and epinephrine.

STATISTICAL ANALYSIS

Multiple paired t tests were used to compare data during MV and SV. Significance was judged according to Bonferroni's inequality, using a (simultaneous) significance level of 0.05; *i.e.*, 0.05 was divided by the number of comparisons to obtain the significance level that an individual P value must satisfy to achieve significance.[13]

Results

The most important finding of our study was that after 10 minutes of SV_1, transmural end-expiratory PAOP had increased from 8 to 25 mmHg ($P < .001$; table 2; fig. 1). In every patient, there was a progressive increase of PAOP, with seven patients showing a marked increase above 20 mmHg (four of seven are included in figure 2). SV was usually accompanied by wheezing and always associated with dyspnea, tachypnea, and progressive ventilatory failure with CO_2 retention, requiring re-institution of mechanical ventilation. In the four patients in whom the LVEDP was measured and compared with end-expiratory PAOP during MV and SV, both pressures were within a few mmHg (fig. 3).

FIG. 1. Weaning of patient 6 from mechanical ventilation (baseline) to spontaneous ventilation (SV₁). There is a progressive increase of pulmonary artery occlusion pressure (PAOP) from 14 mmHg (baseline) to 50 mmHg (9 min SV). The esophageal pressure is reduced during SV with marked negative inspiratory excursions.
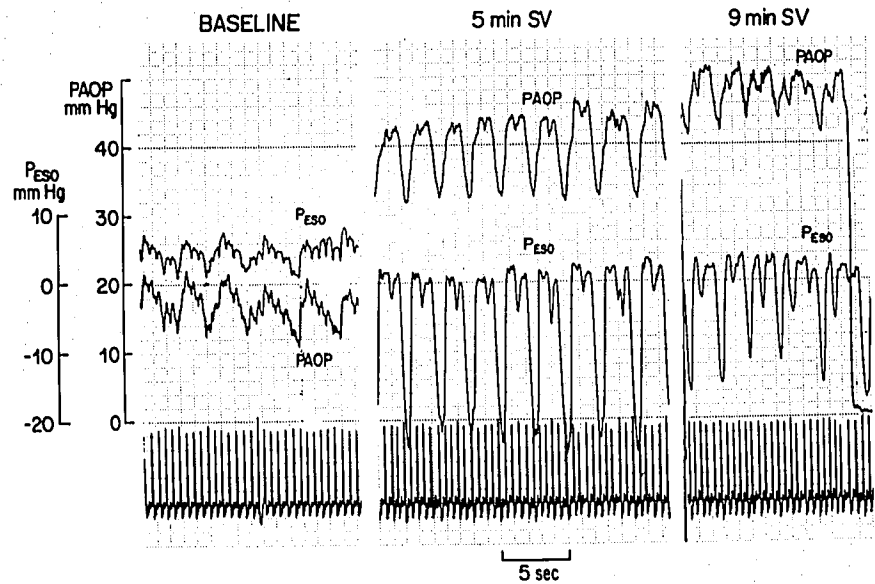
After 10 min of SV₁, esophageal pressure was reduced while cardiac index, heart rate, and central venous, pulmonary, and systemic arterial blood pressures were increased. Although the heart rate increased, the lead II ECG was unchanged. Scintigraphic studies showed the LVEDVI and RVEDVI were increased ($P < .002$), while LVEF and RVEF were unchanged. During SV₁, eight of the 12 patients (patients 1, 3, 5, 6, 8, 10, 11, and 12) had a marked increase of PAOP$_{tm}$ with only a small increase of LVEDVI (fig. 2). Three patients (patients 1, 3, and 9) had scintigraphic

evidence of abnormal LV wall motion during MV which became more severe during SV₁ (for an example, see figure 4A).

There was evidence of acute ventilatory failure during the 10 min of SV₁ (table 2). The Pa$_{CO_2}$ rose from 42 to 58 mmHg ($P < .001$) and the pHa decreased from 7.44 ± 0.04 to 7.32 ± .06. Since the FI$_{O_2}$ during SV₁ was 0.3–0.6, only one patient (patient 6) had a Pa$_{O_2}$ below 50 mmHg during weaning. However, the mean measured arterial oxygen saturation (Sa$_{O_2}$) decreased from 97 ± 2% to 84 ± 15% during SV₁. These mea-

FIG. 2. Changes of transmural pulmonary artery occlusion pressure (PAOP$_{tm}$) and left ventricular end diastolic volume index (LVEDVI) during the transfer from mechanical ventilation (MV) to spontaneous ventilation (SV₁) in 12 patients.
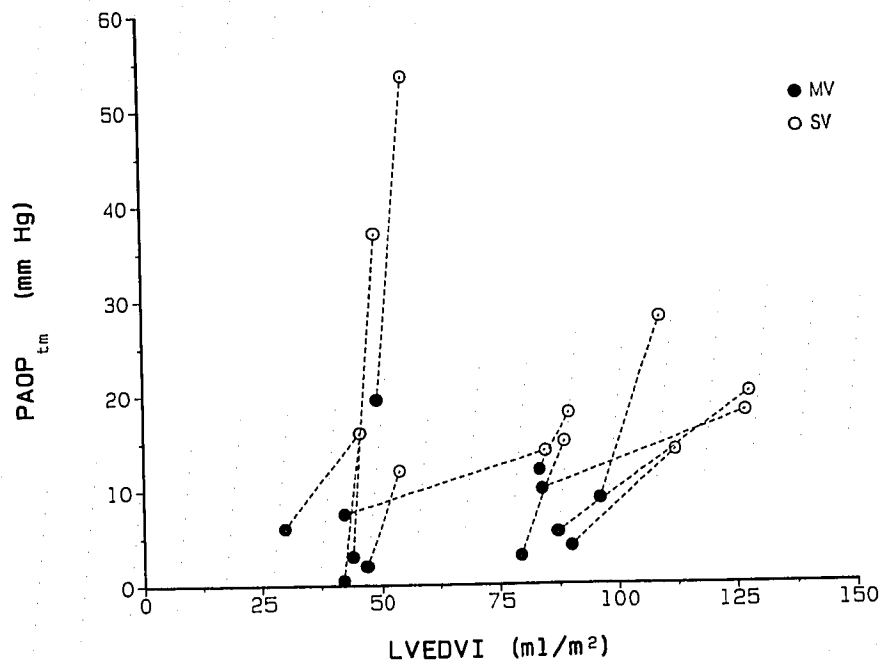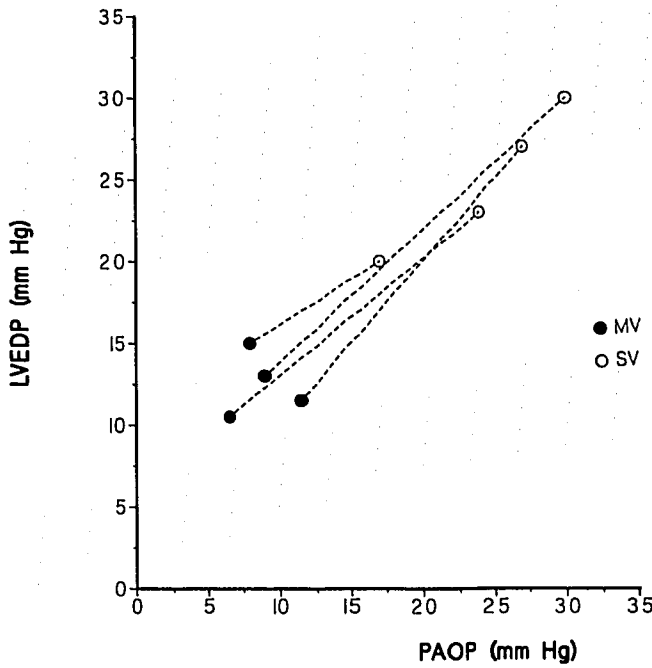
FIG. 3. Correlation between left ventricular end diastolic pressure (LVEDP) and pulmonary artery occluded pressure (PAOP) in four patients during mechanical ventilation (MV) and spontaneous breathing (SV).

surements returned rapidly to the prior control values when the patients were returned to mechanical ventilation.

The mean plasma norepinephrine levels increased from 1.13 ± 0.55 ng/ml (MV) to 1.85 ± 0.96 ng/ml (SV$_1$) ($P < .02$) and epinephrine increased from 0.10 ± 0.05 ng/ml (MV) to 0.20 ± 0.13 ng/ml (SV$_1$) ($P < 0.04$).

One week later, eight of the patients underwent repeat hemodynamic study (SV$_2$) after successful therapy and weaning from mechanical ventilation. At SV$_2$, measurements of tidal volume, respiratory rate, minute ventilation, and inspiratory force were not different than the values measured at the commencement of SV$_1$. The SV$_2$ data listed in table 3 shows mean body weight reduced by 5 kg ($P < .001$) and blood volume decreased from $123 \pm 22\%$ (SV$_1$) to $102 \pm 19\%$ (SV$_2$) of the predicted value. At the time of restudy (SV$_2$), the PAOP$_{tm}$ was maintained at 9 ± 3 mmHg and did not increase.

Discussion

Our study shows that left ventricular filling pressure can increase markedly when weaning from mechanical ventilation is attempted in COPD patients with pre-ex-
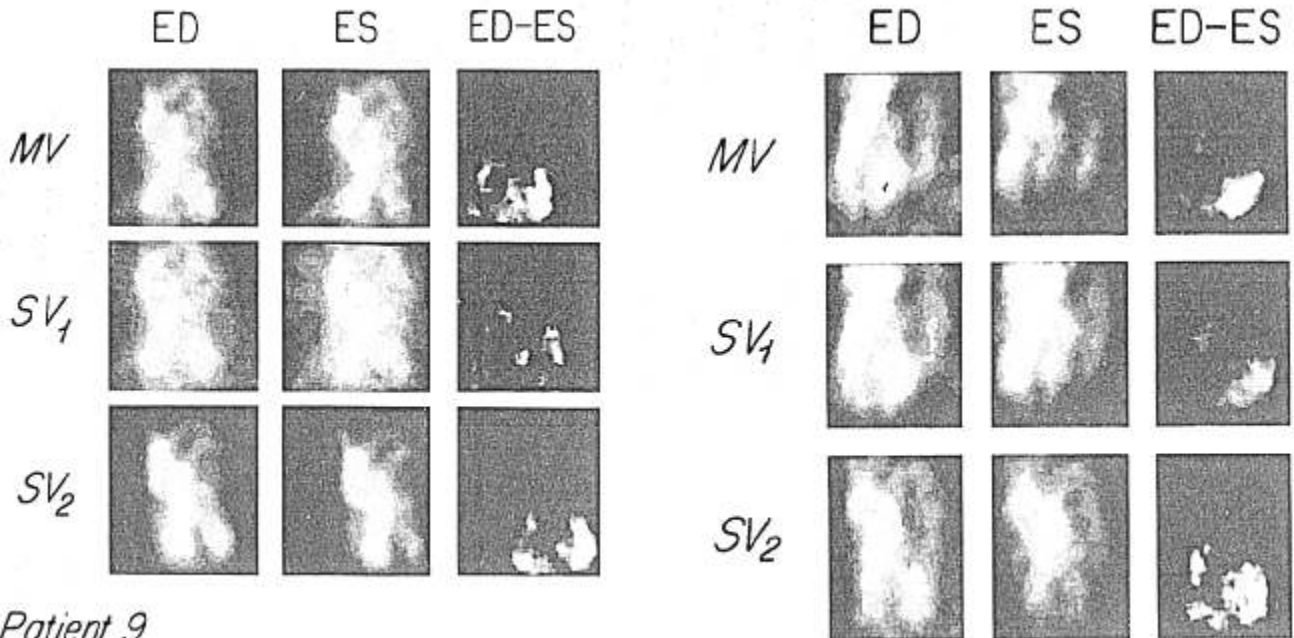
FIG. 4. Cardiac scintiscans during mechanical ventilation (MV) and 30 min later during a period of spontaneous ventilation (SV$_1$), and a follow-up study after 10 days of therapy during spontaneous ventilation (SV$_2$). Images are presented at end diastole (ED) and end systole (ES), with the subtraction image (ED-ES) to provide an estimate of wall motion.

A. Patient 9: Compared with MV during SV$_1$, there is increased end-diastolic and end-systolic biventricular activity with markedly reduced left ventricular (LV) wall motion. After therapy, the SV$_2$ cardiac image is similar to MV, the ventricles are not enlarged, and there is good LV wall motion. B. Patient 2: In comparison to MV during SV$_1$, there is increased end-diastolic and end-systolic biventricular activity with evidence of maintained left ventricular wall motion. After therapy, the SV$_2$ cardiac image is similar to MV, the ventricles are not enlarged, and there is good LV wall motion.

isting heart disease. After 10 min of SV_1, the mean transmural pulmonary artery occlusion pressure increased from 7.5 mmHg to 24.5 mmHg. The $PAOP_{tm}$ increase was progressive and, in seven patients, rose above 20 mmHg. Often, by 5 min of SV_1, the PAOP had increased (fig. 1), but we did not study this systematically. Simultaneously acute respiratory failure occurred, with the mean Pa_{CO_2} increasing 16 mmHg. Our studies cannot dissociate cause from effect, since, by 10 min of SV_1, both acute cardiac and respiratory dysfunction co-existed.

The key event in changing from MV to SV is the shift from a positive intrathoracic pressure to a negative pleural pressure generated by the respiratory muscles. During MV, the mean esophageal pressure, at 5 mmHg (table 2), was probably elevated by the retarded expiratory flow of these COPD patients.[14,15] During SV_1, the mean esophageal pressure was reduced to -2 mmHg and there were large negative inspiratory excursions (e.g., -20 mmHg; fig. 1). These large negative esophageal pressures may be caused by bronchoconstriction during weaning[16] and augmented by the inspiratory airflow resistance of tracheal tubes and the demand valves of mechanical ventilators. Large negative inspiratory pressures could also be due to reductions of static lung compliance, but this is unlikely in COPD patients without alveolar edema or bacterial pneumonia. To minimize demand valve resistance, we selected the Servo 900 C, a ventilator adding minimal inspiratory resistance.[17] In several of these COPD patients, when briefly breathing through a T piece, we measured similar values of Peso suggesting that the major portion of their airway resistance resided in their airways and endotracheal tube. When patients hyperinflated during spontaneous ventilation, large negative distending pressures were required to generate adequate tidal volumes, and Peso decreased.

Reducing intra-thoracic pressure during SV_1 augments venous return, CI, right and left ventricular filling pressures, and end-diastolic volumes of COPD patients (table 2). Studying patient groups with different diseases, others have documented similar but smaller changes accompanying a change from MV to SV.[2,††]

PAOP increased in each patient during SV_1 (table 4). We have obtained evidence in four patients that the PAOP closely reflects the LVEDP during MV and SV (fig. 3); Lockhardt et al. has reported a similar correspondence of pressures in five patients with COPD during exercise.[18] Many of our patients studied with a

†† Fernandez E, Navarrete P, Hinojosa R, Alvarez E, Fornieles H, Valquez G: Trabayo respiratorio y variacions hemodinamicas tras la supresion de la ventilacion mecanica en pacientes afectos de EPOC. Medicina Intensiva 11:123–128, 1987

TABLE 4. Factors Increasing PAOP during Unsuccessful Weaning from MV

1. Increased Preload
   Increased venous return
   • Decreased pleural pressure
   • Sympathetic discharge (stress, hypercapnia)
   Reduced LV compliance
   • Myocardial ischemia
     O_2 Supply reduced
     $\downarrow Pa_{O_2}$, $\downarrow SaO_2$
     $\uparrow$LVEDP and $\uparrow$HR, reducing coronary blood flow
     O_2 Demand increased
     $\uparrow$Catecholamines
     $\uparrow$HR, $\uparrow$Systolic BP
     $\uparrow$Work of breathing
   • LV Enlargement
   • RV Enlargement (ventricular interdependence)
   • Compression of heart chambers by regionally hyperinflated lung
2. Reduced Contractility
   Ischemia
3. Increased Afterload
   $\uparrow$Systolic BP
   $\downarrow$Pleural Pressure

gamma camera had PAOP increases with minimal augmentation of LVEDVI, suggesting reduced LV diastolic compliance.[19] There are several possible causes of a reduced diastolic compliance. Ischemic heart disease was documented in seven of the 15 patients by a history and ECG evidence of myocardial infarction, or by autopsy examination showing severe atherosclerosis of the coronary vessels. LV ischemia can reduce the diastolic compliance, although we noted the lead II ECG was unchanged during weaning.[20]

During SV, several factors favor ischemia due to reduced myocardial O_2 delivery: arteriosclerosis, mild arterial desaturation (84% mean SaO_2 during SV_1), and an increased LVEDP impeding coronary artery flow. Ischemia was also promoted by an increasing myocardial oxygen demand through tachycardia, left and right ventricular systolic hypertension, and catecholamine release.[21] Rasanen et al.[22] observed angina and ischemic ECG changes concomitant with an increased PAOP from 15 to 20 mmHg in patients weaned rapidly from MV to SV after acute myocardial infarction. Three of our patients (patients 1, 3, and 9) had evidence of coronary atherosclerosis and pre-existing abnormal LV and wall motion during MV that became more severe during SV_1 (fig. 4A). Scharf et al. reported that patients with coronary artery disease develop LV dyskinesis during a Mueller maneuver.[23] During SV_1, the markedly negative inspiratory pleural pressure augmented LV afterload and may have promoted LV dyskinesis by the same mechanism.

Robotham and Mitzner have demonstrated that RV engorgement can cause septal flattening and impairment of LV filling with an elevated LVEDP.[24] Re-
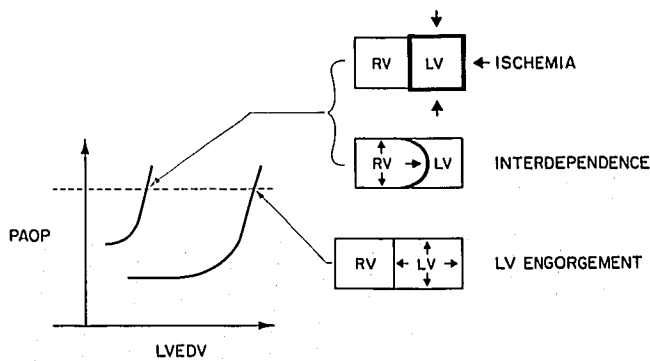
FIG. 5. A schema of several possible mechanisms causing the increased pulmonary artery occlusion pressure (PAOP) during weaning from mechanical ventilation. Increases of PAOP at a smaller left ventricular end-diastolic volume (LVEDV) suggest a reduced ventricular compliance possibly caused by ischemia or right ventricular (RV) enlargement. Increases of PAOP at a larger LVEDV suggest ventricular engorgement.

strained by an indistensible pericardium, both ventricles are interdependent; thus, another possible cause of reduced LV compliance in some of our patients was encroachment upon the left ventricle by a dilated right ventricle. Although the mean values for RVEDVI during SV_1 were not abnormally large, all the patients increased their RVEDVI and six patients developed an RVEDVI exceeding 100 ml/M^2.

Whereas we measured a 12 mmHg absolute increase of PAOP during weaning, Butler *et al.* reported a rise of 4.9 mmHg during exercise of COPD patients.[25] They postulate that the localized regions of hyperinflation that they observed radiographically compress the heart and raise the wedge pressure.

During SV_1, LVEDVI was increased in all patients, minimally in eight, and markedly in four (fig. 2). This places the LVEDP on the steeply ascending portion of the LV pressure-volume compliance curve (fig. 5). Increased LV volume was promoted by a combination of increased venous return and augmented afterload. Afterload was increased by catecholamine release. Increased sympathetic activity was reflected by tachycardia, increased systemic blood pressure, and augmented blood levels of epinephrine and norepinephrine. Kennedy *et al.* also measured increased catecholamines during weaning.[21] LV afterload was also increased by the reduction of pleural pressure.[24,26] Another reason for increasing LVEDVI is an augmentation of venous return, due to the low pleural pressure and peripheral venoconstriction with central translocation of blood volume.

Increased LV filling pressure is a major component of the cascade of events leading to weaning failure. Increased LVEDP may narrow small airways, increasing

airway resistance and the work of breathing, and, thus, precipitating respiratory muscle fatigue. Figure 1 illustrates a decreasing and markedly varying peak negative inspiratory pressure after 9 min of SV_1, suggesting diaphragmatic fatigue. Diaphragmatic fatigue during weaning may occur if the increased blood supply requirements of working respiratory muscles are not provided. Delooz *et al.*[27] and Wolff *et al.*[28] studied patients after heart surgery, and reported that an increase of CI predicted successful weaning. Two of our patients (patients 1 and 6) did not increase their CI during weaning, and neither weaned from the ventilator.

The basis of our treatment with diuretics was to reduce the circulating blood volume, and reduce central transfusion by venoconstriction. Diuretics may also reduce airway edema and resistance.[29] After diuresis (mean weight loss 5 kg), eight patients successfully weaned from the ventilator. At that time (SV_2), their tidal volume, respiratory rate, minute ventilation, and negative inspiratory pressure were not different from SV_1, suggesting that their respiratory function had not improved at the time of restudy (SV_2); however, their $PAOP_{tm}$ was stably maintained at 9 ± 3 mmHg and hemodynamic values were close to those measured during MV.

We believe that forced diuresis allowed many of our patients to wean from the ventilator; however, lacking a control group that was not treated with diuretics, we cannot prove this point. As we learned more about the adverse cardiopulmonary dynamics that occur during weaning, we found ourselves unwilling to withhold therapy and possibly prolong the weaning period. It is possible that, during the week-long period of study, our patients spontaneously improved due to rest of their respiratory muscles or some other unspecified therapeutic event. However, due to the long period of mechanical ventilation in many patients prior to diuretic therapy, we believe spontaneous improvement was most unlikely.

The present studies add a new dimension to the observations of Sladen *et al.*,[30] who demonstrated that water retention during prolonged mechanical ventilation resulted in impaired blood gas exchange. Our studies demonstrate that patients with impaired left ventricular function and chronic obstructive airways disease may suffer a combination of acute left ventricular dysfunction and acute respiratory failure when transferring from MV to SV, despite the lack of evidence of hemodynamic abnormalities during MV. This can be prevented by decreasing the circulating blood volume, indicating that translocation of blood from the peripheral to the central circulation in the presence of LV diastolic dysfunction is probably a major contributing factor to unsuccessful weaning.

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