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Reevaluation of Hemodynamic Consequences of Positive Pressure Ventilation: Emphasis on Cyclic Right Ventricular Afterloading by Mechanical Lung Inflation

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To examine the cyclic changes in right ventricular (RV) function induced by controlled ventilation, right heart catheterization and two-dimensional echocardiography were combined in a group of 20 patients requiring respiratory support for an episode of acute respiratory failure. Simultaneous measurements of RV pressure (using a modified pulmonary artery catheter), RV stroke output (thermodilution), and RV dimensions (two-dimensional echocardiography), permitted a beat to beat evaluation of RV function throughout the mechanical respiratory cycle. When compared with expiration, lung inflation produced an increase in RV systolic pressure and volume, an increase in RV diastolic volume with an unchanged RV diastolic pressure, and a marked decrease in RV ejection fraction. It is concluded that controlled ventilation altered RV function primarily by increasing RV afterload during the lung inflation period. (Key words: Heart, right ventricle: afterload; dimension stroke volume. Lung, ventilation: positive pressure. Measurement techniques: echocardiography.)

HEMODYNAMIC CONSEQUENCES of controlled ventilation have been extensively investigated[1–3] and include a reduction in right ventricular (RV) stroke volume during the inflation period. This decrease in stroke volume has usually been attributed to the decrease in venous return resulting from increased intrathoracic pressure. However, another factor could also play a role; during lung inflation the transpulmonary pressure is suddenly increased[4] and thereby might increase the resistance to flow in all the vessels exposed to alveolar pressure. This factor might be detrimental, particularly when lung disease *per se* increases pulmonary vascular resistance and PEEP is added to ventilatory support.

The present study was undertaken in a group of patients requiring respiratory support for acute respiratory failure to examine whether this potential effect of mechanical lung inflation contributes to decreased RV stroke volume.

Materials and Methods

Twenty patients requiring respiratory support for acute hypoxemic respiratory failure were studied. Respiratory failure resulted from bacterial pneumonia (four patients), inhalation pneumonia (six patients), severe sepsis (six patients), fat embolism (one patient), acute pancreatitis (one patient), major surgical procedure with massive transfusion (one patient), and contrast media-induced pulmonary edema (one patient). Average venous admixture ($\dot{Q}_S/\dot{Q}_T$) was 35 ± 14% and average quasistatic lung and chest wall compliance was 42 ± 16 ml/cmH_2O. Informed consent was obtained from next of kin before the study, and the protocol was consistent with ethical regulations of our hospital. At the time of the study, the lungs of all patients were being ventilated by a ventilator (Bourns Bear One or ATM CPU1®) that delivered a constant tidal volume (8–12 ml/kg of body weight) at a constant inspiratory flow rate and a level of end-expiratory pressure (8 ± 5 cmH_2O) determined as "best PEEP" by calculation of quasistatic lung and chest wall total compliance.[5] During the brief period of the study, patients were sedated with morphine. The respiratory rate of the ventilator was adjusted so that six cardiac beats occurred during a respiratory cycle. An inspiratory to expiratory time ratio of 1:2 was preset so that four cardiac beats (1, 2, 3, and 4) would occur during the expiratory phase of the mechanical cycle and two cardiac beats (5 and 6) would occur during the inspiratory phase of the mechanical cycle. Average heart rate was 110 ± 17 beats per min and average respiratory rate was 18 ± 3 cycles per min.

Hemodynamic Measurements

Pulmonary artery and right ventricular pressures were obtained from previously inserted pulmonary artery triple-lumen balloon catheters (Elecath® 73 R 6067, 7-Fr). Because the proximal port of the pulmonary artery catheter is 14 cm from the tip, RV pressure could be simultaneously recorded. Pleural pressure was measured with an esophageal balloon (5 cm in length and 3.2 cm in circumference) sealed over one end of a polyethylene catheter (inner diameter, 1.4 mm; length, 94 cm). This balloon was advanced through the nose into the esophagus 35–40 cm from the nares, inflated with 10 ml air, and allowed to deflate spontaneously, resulting in a residual volume of approximately 0.2 ml air. Balloon placement was considered correct when the patient was briefly disconnected from the ventilator and a negative pleural pressure was

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recorded. Tracheal pressure was obtained from a sideport of the endotracheal tube. All pressures were measured with Hewlett-Packard® transducers positioned at the midaxillary line, with atmospheric pressure as a zero reference, and were simultaneously recorded with an electrocardiographic (ECG) lead and expired tidal volume on a photographic Honeywell® LS8 multichannel recorder. Vascular pressures were expressed as transmural pressures (*i.e.*, measured pressure minus esophageal pressure). Cardiac output was measured by the thermodilution technique, using the average of five determinations obtained by the injection of 10 ml of room temperature dextrose at regularly spaced intervals throughout the respiratory cycle. Average cardiac index for the whole group was 3.9 ± 0.8 $l \cdot min^{-1} \cdot m^{-2}$.

Echocardiographic Measurements

Image acquisition technique. Echocardiographic recordings were performed using a wide angle, phased-array digital sector scanner (Varian® V 3400 R or Toshiba® SSH 160A). A long axis four-chamber view was obtained in each patient from an apical approach. Echocardiographic images were recorded on videotape, together with an ECG lead and respiratory flow obtained by way of a pneumotachograph, the signal of which was amplified and displayed on the video screen. Precise timing of each cardiac beat within the respiratory cycle could thus be obtained. Echocardiographic recordings were reviewed for single-frame stop–motion analysis of six successive cardiac beats occurring during an entire respiratory cycle. The end-diastolic frame was selected at the peak of the R-wave on the ECG, and the end-systolic frame was defined as the smallest ventricular dimension during the last half of the T-wave.

Quantitative image analysis. Using a microcomputer (Elan AT, Leanord®) interfaced with the video tape player, stop–motion frames at end-diastole and end-systole were digitized and displayed on the microcomputer screen to delineate the endocardial outlines of the right ventricle. RV end-diastolic (ED) and end-systolic (ES) areas (A) of

TABLE 1. Hemodynamic Data

Beat	RVSP (mmHg)	PADP (mmHg)	RVEDP (mmHg)
1	29.3 ± 9.1	16.4 ± 6	8.2 ± 3.3
2	32.6 ± 9.4	16.8 ± 5.9	8 ± 3.3
3	32.7 ± 9.4	16.8 ± 5.9	8 ± 3.3
4	32.7 ± 9.4	16.8 ± 5.9	8 ± 3.3
5	34.1 ± 9.6*	20 ± 6*	8.2 ± 3.3
6	35.3 ± 9.6*	21.4 ± 6*	8.6 ± 3.6

Values are mean ± SD. Beats 1 to 4 occurred during exhalation and beats 5 and 6 occurred during lung inflation. All pressures are transmural pressures.
* $P < 0.05$.

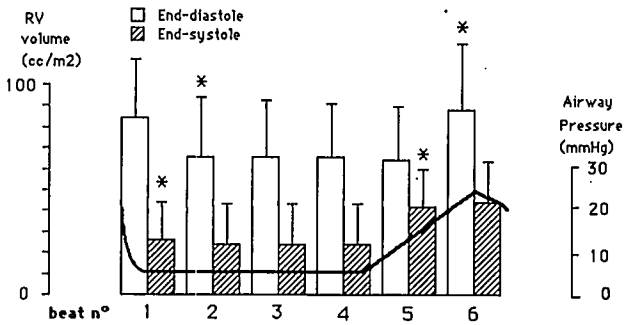

FIG. 1. Changes in RV volumes throughout the respiratory cycle, identified by the mean airway pressure change. Beats 1 to 4 occurred during expiration and beats 5 and 6 occurred during inspiration. Corresponding ejection fractions are as follows: 0.71 ± 0.19,* 0.64 ± 0.15, 0.63 ± 0.14, 0.63 ± 0.15, 0.37 ± 0.10,* and 0.50 ± 0.13.* *$P < 0.05$ *versus* the preceding beat.

the six successive cardiac beats were automatically processed. Stroke area (SA) of each beat was calculated as the difference between EDA and ESA. Stroke areas were averaged during the whole respiratory cycle. Three successive respiratory cycles were analyzed and averaged. Finally, average stroke area was determined using the thermodilution stroke index measured simultaneously. End-diastolic and end-systolic volumes (EDV, ESV) were then calculated by multiplying the corresponding area by the calibration factor. Ejection fractions (EF) were calculated as (EDV − ESV)/EDV.

Statistical Analysis

Statistical analysis concerning beat to beat hemodynamic and echocardiographic measurements during a whole respiratory cycle was performed using the BMDP statistical package. Data are expressed as mean ± SD. Statistical analysis included a two-way analysis of variance (ANOVA) followed by pairwise *t* test using Bonferroni probabilities (beat to beat comparison) or by the contrast method (respiratory time comparison).

Results

Changes in transmural pressures (measured relative to esophageal pressure) throughout the respiratory cycle are reported in table 1. When compared with the expiratory phase (beats 1, 2, 3, and 4), mechanical lung inflation (beats 5 and 6) produced a cyclic increase in RV systolic pressure and in pulmonary arterial diastolic pressure. Transmural RVED pressure also slightly increased, but this change was not statistically significant. Sequential changes in RV volumes and EF throughout the respiratory cycle are shown in figure 1. The first inspiratory beat (beat 5) occurring at the onset of lung inflation was characterized by a markedly reduced RVEF, from 0.63 ± 0.15 (beat 4) to 0.37 ± 0.10 (beat 5). RVESV of this first in-

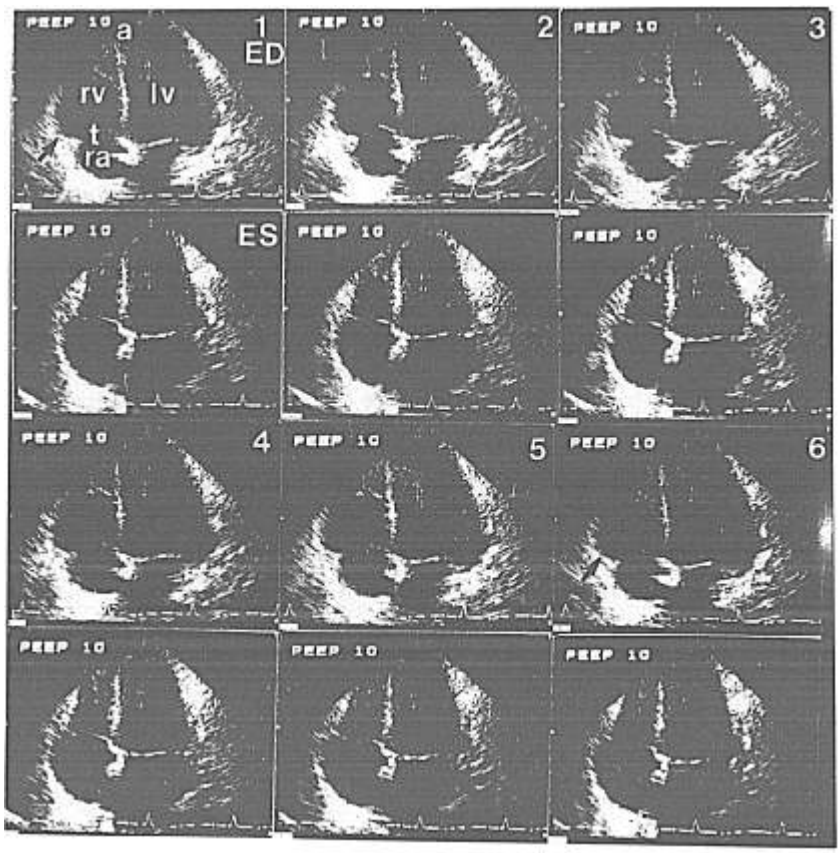

FIG. 2. An example of beat by beat two-dimensional echocardiographic examination at end-diastole (top) and end-systole (bottom). Beats 1 to 4 occurred during expiration and beats 5 and 6 occurred during inspiration: rv = right ventricle; ra = right atrium; t = tricuspid valve; lv = left ventricle; a = apex. The largest RV cavity (arrow) is observed at beats 1 and 6.

spiratory beat was significantly increased. RVEDV of the second inspiratory beat (beat 6) occurring at the end of lung inflation was significantly increased, and the corresponding RVEF increased from 0.37 ± 0.10 (beat 5) to 0.50 ± 0.13 (beat 6). RVESV remained increased and the following RVEDV that corresponded to the first expiratory beat (beat 1) remained elevated. This first expiratory beat was characterized by an increased RVEF from 0.50 ± 0.10 (beat 6) to 0.71 ± 0.19 (beat 1) and a significant reduction in RVESV. RVEDV of the second expiratory beat (beat 2) was reduced and associated with a slight decrease in RVEF from 0.71 ± 0.19 (beat 1) to 0.64 ± 0.15 (beat 2). No other change occurred during the following expiratory beats (3 and 4). An example of two-dimensional echocardiographic studies is given in figure 2.

Discussion

The basic principle of conventional respiratory support lies in using intermittent positive pressure to produce an increase in lung volume. However, due to transmission of the airway pressure to the pleural cavity,[4] tidal delivery produces an intermittent increase in intrathoracic pressure, which in turn reduces the pressure gradient for systemic venous return. This effect is expected to reduce first RV preload and then as an end-result, LV preload, and is widely accepted as the major hemodynamic consequence of respiratory support.[1–3] Blood volume expansion is routinely used to restore cardiac output when RV preload is thought to be excessively decreased by respiratory support.[6] Lower body positive pressure has also been reported to represent an efficient hemodynamic support in this setting.[7] The clinical relevance of another factor thought to reduce LV preload, *i.e.*, leftward septal shift, has also been demonstrated in our previous study.[8]

Reduction of venous return during the inspiratory phase of respiratory support has been extensively documented. Among the numerous studies, those by Hubay *et al.*[9] and Morgan *et al.*,[10] which used implanted ultrasonic flow transducers in dogs, have clearly demonstrated that vena caval blood flow decreased during mechanical lung inflation. The reduction in vena caval blood flow is usually considered to be related to the inspiratory increase in pleural pressure and the causal factor for an actual decrease in RV preload. However, reduction in vena caval blood flow could also have resulted, at least partly, from an impairment in RV systolic function due to an increase in RV output impedance. We have recently reported that a strong relation could be observed during respiratory support between the level of transpulmonary pressure and RV output impedance.[11]

The impedance of the pulmonary vascular bed to RV ejection depends on both compliance and resistance of the pulmonary circulation, and both in turn depend on the state of lung inflation.[12] Lung inflation produces an enlargement of the intrapulmonary (extraalveolar) vessels by radial traction,[12] and this inspiratory increase in vascular size is expected to reduce RV output impedance. However, collapse of intraalveolar vessels in some areas by lung inflation[13] and by increasing pulmonary capillary resistance would exert an opposite effect, *i.e.*, increase RV output impedance. The result in terms of RV afterloading thus depends on the respective contribution of these two opposite effects, which in turn depends on the state of the underlying lung and the amount of tidal volume. Large tidal volumes such as those delivered by mechanical ventilation, or even small tidal volumes superimposed on an elevated end-expiratory lung volume by PEEP, would increase pulmonary vascular resistance. Moreover, any increase in lung volume above functional residual capacity by respiratory support would increase pulmonary vascular impedance in patients with lung disease, in contrast to quiet spontaneous inspiration in normal subjects, which does not significantly affect input impedance of the pulmonary arterial system.[14]

As an illustration of altered mechanical characteristics of pulmonary circulation, during mechanical ventilation one can mention that when hemodynamic support was achieved either by blood volume expansion[8,15] or lower body positive pressure,[7] right atrial pressure and pulmonary artery pressure usually increased to the same extent.[7,8,15] This finding strongly suggests that pulmonary circulation cannot accept increasing blood flow without increasing pressure, thereby hindering right ventricle emptying during systole. Moreover, in a previous study using two-dimensional echocardiography to visualize the interventricular septum (IVS) in patients with severe acute respiratory failure, high levels of PEEP were always associated with RV afterloading in the form of IVS flattening.[8] However, IVS was found to have a normal pattern at baseline and with moderate levels of PEEP (<20 cmH_2O). This finding suggested that during the expiratory phase no significant RV afterloading resulted from diseased lungs or use of moderate levels of PEEP. In contrast, when higher, and probably excessive, levels of PEEP were used, end-systolic septal flattening was clearly demonstrated, a finding usually associated with severe RV afterloading.[16] However, for methodological reasons, only the expiratory phase of the respiratory cycle was analyzed.

In the present study, we used two-dimensional echocardiography, which has been demonstrated to provide a reliable measure of RV size.[17] However, this technique proved to be particularly difficult to implement during mechanical ventilation. Beat to beat echocardiographic recording during the whole respiratory cycle by an apical approach could be obtained only in highly selected patients. Indeed, in many patients left lung inflation obliterated the ultrasonic window during this part of the respiratory cycle. Yet, a subcostal approach would make it possible to record a long-axis view during the whole respiratory cycle in the majority of patients. However, with this subcostal approach the recorded plane is a truncated one and the shift in the position of the heart during lung inflation induces cyclic changes on the recording plane that render RV cavity measurements unreliable. This shift consisted in slight lateral translation parallel to the long axis and was not likely to alter measurements of RV cavity in so far as the latter is visualized on a strict long-axis view. Lack of any significant short-axis rotation during a mechanical respiratory cycle has been previously illustrated by typical recordings obtained from short-axis views, showing that no significant rotation occurred in papillary muscle position.[3]

Our present data support the concept that mechanical lung inflation is associated with an increase in RV afterload. During the inspiratory phase both RV systolic pressure and end-systolic volume increased and therefore are expected to result in an increase in RV systolic wall stress. Accordingly, this finding prompted us to reexamine the part played by RV preload reduction in the hemodynamic consequences of respiratory support. In our patients during lung inflation, RV preload as reflected by RVED volume, was not reduced but actually increased. In addition, RVED transmural pressure increased with lung inflation, although this increase did not reach statistical significance. These findings are at variance with the widely accepted explanation for cardiac output reduction during mechanical respiratory support. However, it should be emphasized that our results were obtained in critically ill patients with damaged lungs, whereas hemodynamic consequences of respiratory support have usually been investigated in animals[2] or in normal subjects.[1] Acute respiratory failure *per se* usually increases pulmonary vascular resistance[18] and also modifies lung compliance, a factor that may alter the transmission of airway pressure to pleural space and in turn the amount of transpulmonary pressure needed to deliver a sufficient tidal volume.[4] Accordingly, hemodynamic effects of lung inflation might be mediated through different mechanisms depending on the presence of lung disease. However, in a previous study performed in adult volunteers with normal lungs, increased functional residual capacity caused by positive pressure airway breathing significantly increased the afterload placed upon the right ventricle.[19]

In conclusion, the current study suggests that mechanical lung inflation by positive airway pressure substantially affects RV systolic function by increasing RV output impedance. RV afterloading was also evidenced in our previous study, which demonstrated leftward systolic and

diastolic septal shift, the latter being responsible for a reduction in LV distensibility. By demonstrating a reduction in RV stroke output and presumably in pulmonary venous return, the present study adds further insight into the cardiovascular effects of positive pressure ventilation. Both factors, *i.e.*, decreased LV inflow and compliance, are expected to act together to reduce LV preload and cardiac output. In patients who exhibit a poor hemodynamic tolerance to positive inspiratory pressure during ventilatory assistance, blood volume expansion is usually indicated and has proven to be effective. Such a therapeutic approach is appropriate because increasing RV preload can in part compensate for RV overloading by an increase in myocardial segment length, resulting in an augmented stroke volume. Furthermore, the present data, if confirmed by further studies, would also provide a rationale for using inotropic agents when blood volume expansion by itself does not fully restore hemodynamic status, especially in patients whose basal RV systolic function is depressed.

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