Cyclic changes in arterial pulse during respiratory support

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ABSTRACT In 13 patients on respiratory support we combined two-dimensional echocardiography with hemodynamic monitoring to determine the mechanism of cyclic changes in arterial pulse, defined as an inspiratory rise in radial artery pulse pressure. Beat-to-beat evaluation of cardiac performance was obtained during the following three distinct consecutive phases of the controlled respiratory cycle: exhalation (phase I), preinspiratory pause (phase II), and lung inflation (phase III). Airway pressure, left ventricular filling pressure (i.e., pulmonary capillary wedge minus esophageal pressure), and pulmonary artery and radial artery pressures were simultaneously recorded during mechanical ventilation along with beat-to-beat two-dimensional echocardiographic left ventricular end-systolic and end-diastolic dimensions. From a reference value for pulmonary artery and radial artery pulse contour obtained during a brief period of imposed apnea, beat-to-beat measurements of left and right ventricular stroke output were also performed during the controlled respiratory cycle with the pulse contour method. Cyclic changes in arterial pulse appeared to result directly from a transitory increase in left ventricular stroke output during lung inflation (41.4 ± 14.6 ml/m²), whereas right ventricular stroke output exhibited a steep fall (31.7 ± 12.4 ml/m²) at this time. An opposite variation was also observed during exhalation, during which a fall in left ventricular stroke output (31.9 ± 11.2 ml/m²) was accompanied by a rise in right ventricular stroke output (38.6 ± 11.9 ml/m²). Both stroke outputs reached an identical level during preinspiratory pause (37.4 ± 14.1 ml/m² for left ventricle and 39.1 ± 13.8 ml/m² for right ventricle). Such an inspiratory increase in left ventricular stroke output during lung inflation was no doubt largely due to a transient improvement in left ventricular preload and this is supported by our finding of a concomitant increase in left ventricular filling pressure and end-diastolic dimensions during the inspiratory phase.


IN CRITICALLY ILL PATIENTS, continuous monitoring consistently demonstrates an inspiratory rise in arterial pressure when respiratory support with mechanically controlled ventilation is used. Often noted in the past, this inspiratory increase in arterial pulse during positive pressure lung inflation has been called "reversed pulsus paradoxus,"2 in contrast with the inspiratory decline in arterial pulse (paradoxical pulse) sometimes observed during spontaneous breathing in cardiac tamponade3 or status asthmaticus4. Such an inspiratory increase in arterial pulse during positive-pressure breathing is quite unexpected since positive-pressure lung inflation, by increasing pleural pressure and lung volume, should act to decrease aortic flow, decrease venous return to the right atrium,5 and increase right ventricular afterload.6 On the other hand, the observed inspiratory increase in blood pressure involves not only the systolic and diastolic pressures, but also the pulse pressure. Therefore, direct transmission of intrathoracic pressure changes to the left ventricle and subsequently into the arterial system cannot totally account for this increase. The following other factors could lead to a rise in arterial pulse during positive-pressure lung inflation: (1) increased pulmonary venous return by the squeezing of blood out of the pulmonary capillaries,2 (2) decreased left ventricular afterload,7 (3) assisted left ventricular performance by the compression of the heart,8 and (4) α-adrenergic discharges that occur in synchrony with lung inflation.9

In order to clarify the hemodynamic events that occur in patients on the mechanically controlled ventilation used daily in our respiratory intensive care unit, we used a combined hemodynamic and two-dimen-
sional echocardiographic technique in a group of critically ill patients who needed hemodynamic monitoring and respiratory support by controlled ventilation.

Material and methods
We studied 13 adult patients (mean age 39 ± 15 years) who needed prolonged respiratory support for adult respiratory distress syndrome (eight patients), neurologic disease (two patients), chronic obstructive pulmonary disease (two patients), or cardiogenic pulmonary edema (one patient). Our study was performed on the second or third day of respiratory assistance. At this time all patients were on a volume-controlled ventilator (Bourns Bear One) that delivered a constant tidal volume (10 to 15 ml/kg body weight). Hemodynamics and blood gases were monitored with indwelling radial and pulmonary artery catheters.

During the brief period of the study (30 to 45 min) patients were sedated with intravenous diazepam and with pancuronium bromide. Respiratory rate of the ventilator was adjusted so that 9 cardiac beats occurred during a whole respiratory cycle. An inspiratory to expiratory time ratio of 1:2 was preset so that 6 cardiac beats would occur during the expiratory phase of the mechanical cycle and 3 cardiac beats would occur during the inspiratory phase of the mechanical cycle. The expiratory phase was subdivided into the following two phases: (1) expiration, which occurred at the onset of the expiratory phase and coincided with beats 1, 2, and 3 (phase I) and (2) preinspiratory pause, which occurred at the end of the expiratory phase and coincided with beats 4, 5, and 6 (phase II). The inspiratory or lung inflation phase, which coincided with beats 7, 8, and 9, was defined as phase III. During the study ventilatory conditions were not very different from those during respiratory therapy. Average heart rate was 100 ± 16 beats/min, and average respiratory rate was 11 ± 2 respiratory cycles per minute. The tidal volume used was 12 ml/kg body weight, resulting in an inspiratory flow of 35 to 50 l/min, with a pause of 0.5 to 0.8 sec at the end of insufflation and preceding expiration.

Systemic arterial, pulmonary capillary wedge, pulmonary arterial, and right atrial pressures were obtained from indwelling radial Teflon and pulmonary Swan-Ganz catheters previously inserted percutaneously for monitoring. Esophageal pressure was measured during the study with an esophageal balloon advanced through the nose into the esophagus and down to 40 cm from the nares. Airways pressure was measured with a special connector inserted in the respiratory circuit close to the endotracheal tube. All pressures were measured with Hewlett-Packard transducers positioned at the midaxillary level, with the use of atmospheric pressure as a zero reference level, and were simultaneously recorded together with an electrocardiographic lead on a photographic Honeywell L86 multichannel recorder. No phase lag between the air- and fluid-filled systems was evident at a respiratory rate three times greater than that used in this study. Cardiac output was measured by the thermodilution technique (Edwards cardiac output computer 9520) and the averaging of three serial determinations.

Beat-to-beat measurement of the left and right ventricular stroke output was obtained with the pulse contour method according to the following formula:

\[ SV = K \cdot Psa \cdot (1 + Ts/Td), \]

where SV is stroke index in milliliters per square meter, K is an arbitrary constant, Psa is the area under the systolic portion of the pressure curve above an horizontal line drawn from the diastolic pressure and bounded by a vertical line through the lowest point in the incisura, Ts is the duration of systole, and Td is the duration of diastole. The Psa term for each pressure contour was obtained from high-speed recordings of radial and pulmonary artery pressures, which were digitized with a Hewlett-Packard 9871 A digitizer and processed for measurement of surface area with a Hewlett-Packard 9825 A desk-top computer. The K constant was initially determined for each patient from simultaneous pressures and thermodilution cardiac output measurements determined during a brief period of apnea, at a time when left and right ventricular stroke volumes were presumably similar, by substituting the measured value for stroke volume and solving the equation for K. The K value thus obtained was used for beat-to-beat calculation of stroke volume during controlled ventilation. Cardiac index was also measured during mechanical ventilation by the thermodilution technique and was correlated with the value computed from the pulse contour method. The latter value was obtained by summing the nine successive values of stroke output computed over an entire respiratory cycle and multiplying them by the respiratory rate.

Echocardiographic studies were performed in patients in the supine left lateral position with a wide-angle phased-array digital sector scanner (Varian V 3400-R). From a left lateral parasternal (nine patients) or subcostal approach (four patients), we selected for study and recorded on a Panasonic NV 8200 videotape recorder a short-axis cross-sectional view of left ventricle at the midpapillary muscle level. Inspiration and expiration during respiratory support caused cyclic changes in cardiac position within the thorax. Thus, we had to change angulation of the transducer slightly during recording of serial echocardiograms to ensure that the short-axis level relative to the papillary muscles remained the same. An electrocardiographic lead was recorded during each study, and respiratory flow was also monitored on the video screen with a disposable pneumotachograph and a McGaw respiratory volume monitor. Precise timing of each cardiac beat within the respiratory cycle could thus be obtained. Two-dimensional echocardiographic tapes were played back for subsequent single-frame stop-motion analysis of the left ventricle short-axis cross-sectional area at both end-diastole (onset of QRS) and end-systole (end of the T wave). Endocardial outlines of end-diastolic and end-systolic cross-sectional areas were directly obtained from hard copy; they were then digitized and processed for measurement of surface areas. The reduction in left ventricular area from end-diastole to end-systole was used as an index of left ventricular stroke output, and the percent area change (end-diastolic area - end-systolic area)/end-diastolic area × 100% was used as an index of left ventricular ejection fraction. During two-dimensional echocardiographic examination special attention was also paid to any eventual spatial change of the interventricular septal configuration. We also occasionally recorded a M mode tracing.

Statistical analysis. Statistical analysis was performed for beat-to-beat measurements. This included a two-way analysis of variance and comparison of each of the three phases by the contrast method.

Results
Beat-to-beat analysis of hemodynamic data measured during the three phases of a respiratory cycle in the 13 patients is summarized in figure 1. Lung inflation (beats 7 through 9) raised esophageal pressure from an infra-atmospheric to a supra-atmospheric level and resulted in an increase in all intravascular pressures. Systemic arterial pulse pressure increased during lung inflation due to a greater increase in systolic than in diastolic radial artery pressure. Pulmonary arterial pulse exhibited an opposite change that resulted from a greater increase in diastolic than in systolic
pulmonary arterial pressure. The decrease in pulmonary arterial pulse during phase III was followed during phase I of the next cycle by a decrease in the radial arterial pulse pressure with a phase lag of 2 beats. An example of the increase in systemic arterial pressure is illustrated in figure 2, upper panel. Apnea abolished cyclic respiratory changes in radial and pulmonary arterial pressures and allowed cardiac output to be measured at a time when left and right ventricular outputs were presumably similar (figure 2, lower panel). Positive pressure inflation also caused an increase in both pulmonary capillary wedge and right atrial pressures relative to atmospheric pressure (figure 1). However, pulmonary capillary wedge pressure increased slightly more than esophageal pressure so that transmural left ventricular filling pressure increased during inflation. In contrast, right atrial pressure increased slightly less than esophageal pressure and consequently transmural right ventricular filling pressure was reduced. An example of these cyclic changes in pulmonary capillary wedge and right atrial pressures is shown in figure 3.

Validity of the pulse contour method for estimation of the left and right ventricular stroke outputs was demonstrated by the close correlation found between the results obtained with the pulse contour method and cardiac index measured by the thermodilution technique during mechanical ventilation (figure 4). Beat-to-beat respiratory changes in left and right ventricular stroke outputs are summarized in figure 5. During phase III left ventricular stroke output increased whereas right ventricular stroke output substantially decreased. In contrast, during phase I right ventricular stroke output gradually reached its preinspiratory level, whereas left ventricular stroke output exhibited a transient fall with a phase lag of 2 beats. At the end of phase II (beat 6) left and right ventricular stroke outputs were virtually the same.

Results of statistical analysis of the main hemodynamic changes during the three phases of the respiratory cycle are listed in table 1. During phase III heart rate and transmural left ventricular filling pressure increased when compared with phase I and II. Right ventricular transmural filling pressure exhibited significant changes in the opposite direction. Left ventricular stroke output significantly increased during lung inflation and decreased during exhalation when compared with the preinspiratory level. Right ventricular stroke output was significantly reduced during lung inflation when compared with the preinspiratory level and was increased during exhalation compared with the reduced inflation level.

Two-dimensional echocardiographic data obtained during the three phases of a respiratory cycle are summarized in table 2 and beat-to-beat analysis within the same respiratory cycle is shown in figure 6. Left ventricular end-diastolic and end-systolic areas significantly increased during phase III and were reduced during phase I when compared with phase II. The reduction of left ventricular cross-sectional area from end-diastole to end-systole, an index of left ventricular stroke output, significantly increased during phase III and significantly decreased during phase I. Percent area change, an index of left ventricular ejection fraction, was not significantly increased during inflation.
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compared with its preinspiratory level. Representative results from beat-to-beat two-dimensional echocardiographic study are shown in figures 7 and 8.

Finally, during echocardiographic study we did not observe any diastolic modification in septal curvature at any point in the respiratory cycle, as illustrated by an example in figure 7.

Discussion

In 1973 Massumi et al. emphasized that, in man, an inspiratory rise of the arterial systolic and diastolic pressures occurs during mechanical ventilation and that this is presumably related to an inspiratory increase in left ventricular stroke output. They called these phasic cyclic changes in systemic arterial pulse reversed pulsus paradoxus and reported them as unusual. The discovery of this phenomenon was in fact not really new; its existence had already been established, particularly in the works by Courand, Werko, and Morgan et al. In our experience, hemodynamic data from patients being mechanically ventilated with intermittent or continuous positive airways pressure convinced us that this phenomenon occurred.

Previous investigators have also established that respiratory changes in systemic arterial pulse during mechanical ventilation were accompanied by changes in the opposite direction in pulmonary arterial pulse, which exhibited a decrease during lung inflation. As expected, these phasic opposite changes were also observed in our study. In animal experiments, availability of direct measurements of aortic and pulmonary artery flows provided a demonstration of changes in pulse that directly reflected the same changes in flow. Despite some conflicting results, the majority of authors on this subject, believe that lung inflation increases the left and reduces the right ventricular stroke output. But, as inflation progresses, left ventricular stroke output decreases secondarily as a result of reduced right ventricular stroke output, which is followed by left ventricular stroke output after a phase lag of 1 or 2 beats. Direct measurement of aortic and pulmonary artery flow was not possible in clinical studies until recently. However, with current technology, direct beat-to-beat estimation of systemic and pulmonary flow is possible with Doppler investigational techniques. In this study we used the pulse

FIGURE 2. Example of a simultaneous recording of an electrocardiogram; radial artery (RA), pulmonary artery (PA), airways (A), and esophageal (E) pressures; and the thermodilution curve (CO th). Top, Periodic lung inflations, as evidenced by a simultaneous increase in airways and esophageal pressures, resulted in cyclic changes in radial artery systolic, diastolic, and pulse pressures (the so-called reversed pulsus paradoxus). The pulmonary artery also exhibited cyclic changes in synchrony with lung inflation. Bottom, A brief apnea period was induced. During this period, esophageal and airways pressures remained at their baseline levels and cyclic changes in radial and pulmonary pulse disappeared. A steady-state measurement of cardiac output was obtained.
contour method in an attempt to indirectly evaluate left and right ventricular stroke outputs. The accuracy of this method has not always been appreciated in the past.17-19 Provided there is a precise measurement of a reference value during apnea, we assumed that the pulse contour method was sufficiently accurate in evaluating beat-to-beat quantitative changes in left and right ventricular stroke outputs. Our assumption was corroborated by the finding of a close correlation between the indirectly calculated value for cardiac output by the pulse contour method and the direct measurement obtained by the thermodilution technique. In addition, our results concerning the left ventricle that were obtained by two-dimensional echocardiography were consonant with those obtained by the pulse contour method. Accordingly, we suggested that a brief lung inflation by positive airway pressure might result in an increase in left ventricular stroke output and a concomitant decrease in right ventricular stroke output.

The cyclic changes in right ventricular stroke output observed in this study are different from those observed during spontaneous breathing, during which right ventricular stroke output increased at inspiration.20 Decrease in right ventricular stroke output during positive-pressure lung inflation has been well documented and essentially results from decreased right ventricular filling in this respiratory phase. During mechanical ventilation, rise of pleural pressure to a supra-atmospheric level at inspiration impedes venous return to the right atrium. Our finding of a decreased right ventricular filling pressure during lung inflation is consonant with a decreased venous return at this respiratory phase. In addition, another factor appears to reduce

### TABLE 1
Comparison of hemodynamic data by two-way analysis of variance

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>I vs II</th>
<th>I vs III</th>
<th>II vs III</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>99 ± 16</td>
<td>99 ± 16</td>
<td>103 ± 16</td>
<td>NS</td>
<td>&lt;.025</td>
<td>&lt;.025</td>
</tr>
<tr>
<td>LVFP (PCWP - EP, mm Hg)</td>
<td>12.2 ± 5.5</td>
<td>12.6 ± 5.4</td>
<td>14.2 ± 7.2</td>
<td>NS</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>RVFP (RAP - EP, mm Hg)</td>
<td>8.3 ± 4.8</td>
<td>8.4 ± 4.7</td>
<td>7.5 ± 6.3</td>
<td>NS</td>
<td>NS</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>LVPQ (pulse contour method, ml/beat/m²)</td>
<td>31.9 ± 11.2</td>
<td>37.4 ± 14.1</td>
<td>41.4 ± 14.6</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RVFI (pulse contour method, ml/beat/m²)</td>
<td>38.6 ± 11.9</td>
<td>39.1 ± 13.8</td>
<td>31.7 ± 12.4</td>
<td>NS</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

All values are mean ± SD.
HR = heart rate; LVFP = left ventricular filling pressure; PCWP = pulmonary capillary wedge pressure; EP = esophageal pressure; RVFP = right ventricular filling pressure; RAP = right atrial pressure; LVPQ = left ventricular stroke index; RVFI = right ventricular stroke index. *p < .01 for comparison between left and right stroke index.
FIGURE 4. Cardiac index calculated with beat-to-beat measurements of stroke index by the pulmonary artery pulse contour method (PAPM) (left) or by the radial artery pulse contour method (RAPM) (right) was plotted against the value obtained by the thermodilution method (CIp) during respiratory support. A significant linear correlation (solid line) was found in both cases ($r = .95$). The dotted line is the identity line.

TABLE 2
Comparison of two-dimensional echocardiographic data by two-way analysis of variance

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>I vs II</th>
<th>I vs III</th>
<th>II vs III</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDA (cm$^2$)</td>
<td>16.0±4.7</td>
<td>16.9±4.7</td>
<td>19.2±5.9</td>
<td>&lt;.05</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LVESA (cm$^2$)</td>
<td>10.0±4.0</td>
<td>10.2±4.2</td>
<td>10.9±3.6</td>
<td>NS</td>
<td>&lt;.025</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>LV (ED − ES)A (cm$^2$)</td>
<td>6.0±3.9</td>
<td>6.7±3.6</td>
<td>8.3±4.0</td>
<td>&lt;.05</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>% Area change$^a$</td>
<td>37.5±17.9</td>
<td>39.6±17.8</td>
<td>43.2±14.0</td>
<td>NS</td>
<td>&lt;.025</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD. LVEDA = left ventricular end-diastolic area; LVESA = left ventricular end-systolic area; LV(ED − ES)A = area difference between diastole and systole (an index of LV stroke output).

$^a$An index of LV ejection fraction.

right ventricular outflow during lung inflation — the increase in pulmonary vascular resistance when lung volume increases above functional residual capacity. The effect of this factor, observed as a slight increase in pulmonary artery diastolic pressure, remains small as long as controlled ventilation with intermittent positive pressure is used. In this study the two-dimensional echocardiographic changes in septal shape that suggest right ventricular overload were not demonstrated throughout the respiratory cycle. Nevertheless, when controlled ventilation with constant positive pressure was used, which allowed an increase in functional residual capacity, right ventricular afterloading at end-expiration was demonstrated and a superimposed cyclic lung inflation could then transiently enhance right ventricular afterloading. This may explain the particular magnitude of reversed pulsus paradoxus observed under positive end-expiratory pressure.
ship between lung volume and right ventricular after-loading has also been recently illustrated in a clinical study of bronchial asthma\(^2\) in which a decrease in pulmonary artery pulse was found at inspiration, despite a facilitated venous return to the right heart by a very negative pleural pressure.

In accord with previous studies\(^9\),\(^13\),\(^14\) the inspiratory reduction in pulmonary arterial flow observed in this study was followed after a phase lag of 2 beats by a reduction in systemic arterial flow, which began at the end of inhalation and was consequently pronounced during exhalation. Thus, reversed pulsus paradoxus

**FIGURE 6.** Average values for nine successive beat-to-beat echocardiographic measurements recorded over an entire respiratory cycle. Values obtained include those of left ventricular end-diastolic area (ED), left ventricular end-systolic area (ES), and the difference between end-diastolic and end-systolic areas, which was used as an index of left ventricular stroke output. I = phase I of the respiratory cycle (exhalation); II = phase II of the respiratory cycle (preinspiratory pause), and III = phase III of the respiratory cycle (lung inflation). Values are ± SEM. For statistical significance see table 2.

**FIGURE 7.** Example of nine successive two-dimensional echocardiographic end-diastolic frames of both ventricles obtained in the subcostal cross-sectional views. Precise timing of each cardiac beat within the respiratory cycle is illustrated in the right hand corner of each Polaroid print. An electrocardiographic lead and the respiratory flow were simultaneously recorded. From left to the right, beats 1, 2, and 3 occurred during phase I, beats 4, 5, and 6 occurred during phase II, and beats 7, 8, and 9 occurred during lung inflation.
may be described as a transient increase in systemic arterial pulse during lung inflation immediately followed by a decrease at onset of exhalation. Many factors could lead to a rise in radial artery pulse during positive-pressure inflation including decreased left ventricular afterload by increasing pleural pressure, assisted left ventricular performance by the compression of the heart, \( \alpha \)-adrenergic discharges occurring in synchrony with inflation and improving the inotropic state of the left ventricle, and increased pulmonary venous return by the squeezing of blood out of the pulmonary capillaries. In our study, a slight but significant increase in heart rate was observed during lung inflation that probably reflected an increase in sympathetic drive during this respiratory time. The parallel increase in systolic arterial pressure and in end-systolic left ventricular area, together with the minor changes observed in left ventricular ejection fraction, would tend to minimize the role of decreased left ventricular afterload, assisted left ventricular performance, or increased inotropic state by lung inflation. On the other hand, the large increase in left ventricular end-diastolic area observed in this study supports the concept of an increased pulmonary venous return to the left heart during lung inflation. Thus, the purpose of this study was to determine the effect of lung inflation on left ventricular filling. The intensity of this effect depends in part on an indirect effect on venous return and in part on a direct effect on the capacitance of the pulmonary vascular bed. The effect of lung inflation on the capacitance of the pulmonary vascular beds has been analyzed in other studies. Howell et al. hypothesized that the pulmonary vascular bed consisted of two compartments, one that expanded and one that was compressed as lung volume increased. Macklin observed that the capacity of the pulmonary arteries and veins increased during alveolar inflation, but that this increase was not sufficient to equal the volume of fluid entering the arteries and veins in reflux from the squeezed capillaries. In this study we observed an increase in both left ventricular filling pressure and diastolic dimension during lung inflation. Thus, consonant with previous results of Howell et al. and Macklin, we suggest that lung inflation might reduce the capacitance of pulmonary vascular bed and might allow the squeezing of blood from capillaries into the left ventricle. Such a transient increase in preload may improve left ventricular performance and induce a transient increase in left ventricular stroke output.

References

Cyclic changes in arterial pulse during respiratory support.
F Jardin, J C Farcot, P Gueret, J F Prost, Y Ozier and J P Bourdarias

Circulation. 1983;68:266-274
doi: 10.1161/01.CIR.68.2.266
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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