Study objectives: To assess the safety of frequent pressure-volume (PV) curve measurement in patients with acute lung injury (ALI)/ARDS.

Design: Prospective observational study.

Setting: Academic medical-surgical critical care unit.

Patients: Consecutive patients with ALI or ARDS.

Interventions: Static inspiratory PV curves of the respiratory system were determined twice on day 1, then once daily for up to 6 days using a syringe. At each time point, three separate measurements of the PV curve were made. A 100-mL graduated syringe was used to inflate patients' lungs with 50- to 100-mL increments up to an airway pressure of 45 cm H₂O or a total volume of 2 L; each volume step was maintained for 2 to 3 s until a plateau airway pressure was recorded. Outcome measures were mean arterial BP, heart rate (HR), and oxyhemoglobin saturation (SpO₂) prior to and immediately after PV curve measurement. There were *a priori* criteria for procedure discontinuation if poorly tolerated.

Measurements and results: Eleven patients were enrolled with a total of 134 PV curves generated. SpO₂ was 93 ± 4% (mean ± SD) before and fell to a nadir of 89 ± 5% during PV curve measurement (p < 0.001), but increased to 97 ± 4% immediately afterwards (p < 0.001, before vs after). HR rose from 106 ± 22 to 108 ± 22 beats/min immediately after the maneuver (p < 0.001). Mean arterial BP was 93 ± 15 mm Hg before and 100 ± 17 mm Hg immediately afterwards (p < 0.001). During PV curve measurement, systolic BP in one patient fell to 64 mm Hg from 113 mm Hg in another patient, SpO₂ dropped to 79% from 89%. Both changes were transient. The study was discontinued in one patient because of inability to tolerate zero positive end-expiratory pressure; in another patient, the study was discontinued because of the development of subcutaneous emphysema.

Conclusions: PV curve measurement by syringe technique is well tolerated in most patients. Nonetheless, the maneuver may cause significant changes in oxygenation and/or hemodynamics, necessitating close monitoring.

Key words: acute lung injury; ARDS; mechanical ventilation; static pressure-volume curve

Abbreviations: ALI = acute lung injury; FIO₂ = fraction of inspired oxygen; HR = heart rate; LIP = lower inflection point; PEEP = positive end-expiratory pressure; PV = pressure volume; SpO₂ = oxyhemoglobin saturation; UIP = upper inflection point
point (UIP), respectively. Although the significance and reproducibility of these points remains controversial, it has been proposed that the LIP represents the pressure at which collapsed airways and alveoli begin to open, resulting in an abrupt increase in respiratory system compliance. In turn, the UIP has been theorized to represent the pressure at which alveolar overdistension begins to occur, leading to decreased compliance.

Interest in these concepts has grown with the observation that mechanical ventilation, the main therapy for ARDS, can itself worsen lung injury. Ventilator-induced lung injury has been demonstrated to occur both from excessive tidal volumes and lung overdistension (volutrauma), as well as repeated opening and closing of lung units (atelectrauma).

It is in this context that so-called lung-protective ventilation strategies have been explored for the treatment of ARDS. It has been proposed that positive end-expiratory pressure (PEEP) be maintained above the LIP to prevent alveolar collapse, and that plateau pressure be kept below the UIP to prevent alveolar overdistension. Although there are theoretical and experimental data that demonstrate that this proposal is not correct, a randomized trial in patients with ARDS demonstrated a decrease in mortality when this strategy was used. Amato and colleagues compared a strategy of low tidal volumes and PEEP set above the LIP, with a strategy of larger tidal volumes and PEEP based on oxygenation, independent of the PV curve. The low tidal volume and titrated PEEP strategy was associated with a significantly lower mortality compared to the control group. Although this study has been criticized for the high mortality and barotrauma rates in the control arm, its results have renewed interest in the measurement of PV curves in patients with ARDS.

Because respiratory system mechanics in patients with ARDS may change rapidly over the course of the illness, multiple PV curve measurements over time may be required to appropriately adjust ventilatory settings. Little data exist regarding the safety of PV curve measurement in ALI/ARDS, especially in the setting of repeated measurements over time. Hence, the objective of this study was to prospectively monitor the effect of repeated PV curve measurements on oxygenation and hemodynamics of patients with ALI/ARDS.

**Materials and Methods**

This study was part of a larger prospective investigation of the temporal change in PV curves in patients with ARDS. Written informed consent was obtained from all patients or their next-of-kin. The study protocol was approved by the Mount Sinai Hospital research ethics board. All patients admitted to the ICUs who were intubated and receiving mechanical ventilation and met all of the criteria for ALI or ARDS proposed by the American-European Consensus Conference were eligible. Exclusion criteria were use of nonconventional mechanical ventilation (eg, high-frequency ventilation, prone positioning, inhaled nitric oxide); intubation for asthma or a history of obstructive airways disease; inability to tolerate zero PEEP (oxyhemoglobin saturation [SpO2] < 90% on fraction of inspired oxygen [FiO2] of 1.0); hemodynamic instability (systolic BP < 90 mm Hg on vasopressor agents); presence of a tube thoracostomy or other evidence of air leak; pregnancy; or significant renal or hepatic dysfunction (serum creatinine > 110 mol/L or serum bilirubin > 20 mol/L, respectively). The last two exclusion criteria (renal and hepatic dysfunction) were designed to minimize the risk of prolonged neuromuscular blockade from the paralytic agents required during the study.

Static inspiratory PV curves of the respiratory system were determined using a modified super-syringe technique. A calibrated syringe (5510 Series 100 mL Calibrated Syringe; Hans Rudolph; Kansas City, MO) was used in place of a typical 2-L syringe during PV curve determination (Fig 1). The calibrated syringe has 20-mL volume markers along the shaft of the piston plunger, and a sliding lock-ring mechanism to selectively restrict the movement of the shaft. By securing the lock-ring at the desired volume position, the user can limit the excursion of the piston and thereby ensure the delivered volume with each stroke. This type of syringe eliminates the need for a pneumotachograph in the system because the volume of each bolus is known.

In preparation for the maneuver, PEEP was reduced to zero, and the FiO2 was titrated to maintain SpO2 > 90%. Once the SpO2 had stabilized (about 15 minutes later), patients were disconnected from the ventilator and the 100-mL calibrated syringe, filled with 100% oxygen, was connected to the proximal end of the endotracheal tube at end-expiration. Starting from zero PEEP, the patients' lungs were inflated with 500-mL increments.

**FIGURE 1.** Both a bidirectional valve (top and bottom valve) and a unidirectional valve (right arrow) are utilized as shown. Fresh gas supply (100% oxygen) flows through valve 1 (bottom), filling the syringe. As the piston is withdrawn, the resultant negative pressure closes valve 1 (up arrow) to the atmosphere and aspirates only the fresh gas supply into the syringe. Valve 2 also closes in this phase to prevent aspiration of gas from the patient. On forward movement of the piston, valve 1 (down arrow) closes to the oncoming fresh gas supply and instead vents the fresh gas to the atmosphere for the duration of this phase (through top). Valve 2 opens (right arrow) and allows gas into the patient endotracheal tube (ETT). A pressure monitor line is connected to the valve system proximal to the endotracheal tube and is externally monitored.
of 100% oxygen from the syringe until 400 mL had been injected, followed by additional increments of 100 mL until an airway pressure of 45 cm H₂O or a total insufflated volume of 2 L was achieved. Each volume step was maintained until a relatively constant plateau airway pressure was recorded (usually after 2 to 3 s). Airway pressure was recorded using a transducer (Validyne MP45; Validyne Engineering; Northridge, CA) referenced to atmospheric pressure, and a pressure-time curve was generated in real-time. A PV curve was then generated based on the known volumes injected from the syringe and the plateau pressures that had been measured. LABDAT and ANADAT software (RHT-Infodat; Montreal, Canada) on a bedside personal computer were used for data collection and generation of the curves.

One investigator performed the PV curve measurements, while another monitored the patient’s vital signs and oxygen saturation. Following each maneuver, baseline mechanical ventilation was resumed without PEEP for several minutes in order to maintain a constant volume history. All patients received chemical sedation and neuromuscular blockade to ensure that passive PV curves were obtained. PV curves were recorded twice on the first day, approximately 10 h apart (8 AM and 6 PM), followed by once a day (at approximately 8 AM) for up to 6 days. At each time point, three separate measurements of the PV curve were made.

The outcome measures used to assess safety were mean arterial BP, heart rate (HR), and SpO₂ assessed prior to and immediately after PV curve measurements. The nadir in SpO₂ during the maneuver was also measured. Mean arterial BP and HR were determined from an indwelling arterial line, and SpO₂ was measured with a pulse oximeter. If systemic hypotension (defined as systolic BP < 90 mm Hg) occurred during measurement of the PV curve, the procedure was discontinued and the patient received manual ventilation with 100% oxygen, was administered an IV bolus of 500 mL of normal saline solution (if not contraindicated), and then received mechanical ventilation at baseline settings. If the SpO₂ fell to < 95% during PV curve measurement, the procedure was similarly discontinued and the patient received manual ventilation with 100% oxygen before being returned to mechanical ventilation at baseline settings. In either case, the PV curve measurement was reattempted 15 min later; if either complication recurred, the study was discontinued until the following day. The study was terminated prematurely if the patient had hypotension or hypoxemia develop during PV curve measurement on 2 successive days. The study was also terminated if the patient’s respiratory status was improving and the patient was being weaned or extubated, or if the patient’s physician or surrogate decision maker requested that the patient be withdrawn from the study.

In a random, blinded sequence, all PV curves were subsequently examined by three critical care physicians on three different occasions to determine the percentage of PV curves in which the LIP and UIP could be identified (Fig 2). Physicians were given the same standardized instructions: (1) Using a ruler, draw a straight line through the central and most linear segment of the curve (line A); (2) Draw a second straight line (line B) that best fits the data points below the linear segment (the LIP is the pressure at which the two lines intersect, or the pressure corresponding to the point where the slope of the PV curve changes abruptly); and (3) Draw a third straight line (line C) that best fits the data points above the linear segment (the UIP is the pressure where this third line intersects the first line drawn).

**Statistical Analysis**

Mixed-model, repeated-measures analysis for longitudinal data was used to determine if HR, mean arterial BP, and SpO₂ were significantly different before PV curve measurement compared to after PV curve measurement. The nadir values of SpO₂ during the maneuvers were also compared to the values for SpO₂ before and after PV curve measurement. Since measurements were taken repeatedly over time, a first-order autoregressive covariance structure was specified to model the covariance within subjects. This structure implies that adjacent observations on the same subject have a higher correlation than observations that are farther apart. A local influence analysis for the detection of influential subjects was also examined. All analyses were performed using statistical software (SAS version 8.0 for Windows; SAS Institute; Cary, NC); p < 0.05 was considered statistically significant. All data are presented as mean ± SD.

**Results**

Eleven consecutive patients were recruited into the trial (5 women). A total of 134 PV curves were obtained. Mean age was 53 ± 15 years, the mean APACHE (acute physiology and chronic health evaluation) II score on entry into the study was 25 ± 6, and mean lung injury score was 3.0 ± 0.2. The mean PaO₂/FIO₂ at entry was 160 ± 37 mm Hg. Ten of the 11 patients met the criteria for ARDS. The ventilatory parameters immediately prior to the trial are presented in Table 1. Seven of the 11 patients were receiving pressure-control ventilation, 3 patients were receiving pressure-support, and 1 patient was receiving mechanical ventilation using pressure-regulated volume control.

Each recording of the PV curve was completed in 60 to 90 s. Oxygen saturation averaged 93 ± 4% before PV curve measurement, fell to a nadir of 89 ± 5% during the maneuver, and increased to 97 ± 4% immediately afterwards (Fig 3). HR was 106 ± 22 beats/min before, and rose to 108 ± 22 beats/min immediately after PV curve measurement.
(Fig 4). Mean arterial BP was 93 ± 15 mm Hg before the maneuver, and rose to 100 ± 17 mm Hg immediately afterwards (Fig 5). BP, HR, and SpO\textsubscript{2} were significantly different after PV curve measurement compared to before the maneuver (p < 0.001). In addition, the nadir in SpO\textsubscript{2} during PV curve measurement was significantly different from the SpO\textsubscript{2} observed before the maneuver (p < 0.001).

During PV curve measurement in one patient (patient 2), the systolic BP fell from 113 to 64 mm Hg; in another patient (patient 5), the oxygen saturation dropped from 89 to 79%. Because both of these changes were transient, they did not require termination of the study.

The study was discontinued in two patients. The first patient (patient 10) was withdrawn because of inability to tolerate zero PEEP (desaturation to 88% on F\textsubscript{io}2 of 1.0), which occurred in preparation for PV curve measurement on day 4 of the study. In the second patient (patient 1), subcutaneous emphysema developed on day 4 of the study, and by day 6, was believed clinically to have worsened. As a consequence, the study was discontinued although there was never any radiographic evidence of pneumothorax and tube thoracostomy was never required. Five of the 11 patients survived and were discharged from the ICU.

On average, the three physicians were able to identify the LIP and UIP in 92% (range, 90 to 94%) and 64% (range, 63 to 68%) of PV curves, respectively.

**Discussion**

In the original description of ARDS, Ashbaugh and colleagues\textsuperscript{17} commented on the loss of lung compliance associated with the syndrome. In 1975, Suter and colleagues\textsuperscript{18} observed that the addition of PEEP caused an increase in respiratory system compliance to a certain point, after which compliance fell. They postulated that the PV curve in ARDS was shifted from normal, hypothesizing a sigmoidal curve with a lower inflection point. Mata-mis and colleagues\textsuperscript{5} documented the presence of such an inflection point in patients with ARDS, and proposed that the LIP represented the reopening of collapsed lung units. They concluded that determination of the inflection point on the PV curve might be helpful in determining the optimal level of PEEP. In an analogous fashion, some investigators\textsuperscript{2} have suggested that keeping airway pressures below the UIP may be useful in avoiding overdistension of lung units. Given our increasing appreciation of volutrauma and atelectrauma, the notion that PV curve measurement may allow for the titration of mechanical ventilation in a given patient seems appealing.

Indeed, the publication of a randomized controlled trial\textsuperscript{9} in which lung-protective ventilation (tidal volume and PEEP based on the PV curve) was compared to conventional mechanical ventilation has renewed interest in ARDS. This study was notable in that it was the first randomized trial to demonstrate a mortality benefit in ARDS using a specific ventilatory strategy: mortality at 28 days was 33% lower in the lung-protective study arm than in the study arm receiving conventional mechanical ventilation. Although these findings have yet to be reproduced and the study has been criticized,\textsuperscript{19} its publication revived interest in individualized bedside physiology in the titration of mechanical ventilation.\textsuperscript{20}

We\textsuperscript{11} and others\textsuperscript{5} have demonstrated that the PV curve changes over the course of illness in ARDS. If PV curve measurement is to be useful in the titration

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**Table 1—Baseline Patient Demographics and Ventilatory Parameters**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Age</th>
<th>Cause of Lung Injury</th>
<th>APACHE II Score</th>
<th>Pao2/Fio2</th>
<th>Fio2</th>
<th>PEEP, cm H2O</th>
<th>Plateau Pressure, cm H2O</th>
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<tr>
<td>1</td>
<td>Male</td>
<td>37</td>
<td>Alveolar hemorrhage</td>
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<td>245</td>
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<td>12.5</td>
<td>33</td>
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<tr>
<td>2</td>
<td>Female</td>
<td>41</td>
<td>Sepsis/acute myelogenous leukemia</td>
<td>24</td>
<td>172</td>
<td>.35</td>
<td>10</td>
<td>22</td>
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<tr>
<td>3</td>
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<td>49</td>
<td>Pneumonia</td>
<td>22</td>
<td>120</td>
<td>.50</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>65</td>
<td>Perforated bowel/sepsis</td>
<td>25</td>
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<td>.60</td>
<td>8</td>
<td>28</td>
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<td>75</td>
<td>Pneumonia</td>
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<td>124</td>
<td>.50</td>
<td>12</td>
<td>22</td>
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<td>48</td>
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<td>118</td>
<td>.50</td>
<td>12</td>
<td>26</td>
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<td>Pneumonia</td>
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<td>.45</td>
<td>12</td>
<td>40</td>
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<td>9</td>
<td>Female</td>
<td>78</td>
<td>Amiodarone toxicity</td>
<td>24</td>
<td>138</td>
<td>.40</td>
<td>10</td>
<td>26</td>
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<tr>
<td>10</td>
<td>Male</td>
<td>54</td>
<td>Pneumonia</td>
<td>20</td>
<td>145</td>
<td>.40</td>
<td>15</td>
<td>31</td>
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<tr>
<td>11</td>
<td>Female</td>
<td>36</td>
<td>Overdose</td>
<td>5</td>
<td>183</td>
<td>.45</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>53 (15)</td>
<td></td>
<td></td>
<td>23 (6)</td>
<td>160 (37)</td>
<td>.48 (.05)</td>
<td>11 (11)</td>
<td>30 (6)</td>
</tr>
</tbody>
</table>

*APACHE = acute physiology and chronic health evaluation.
of mechanical ventilation, it is likely that such curves will have to be measured more than once. However, the safety of repeated measurements of the PV curve in patients with ARDS has yet not been established.

Our data demonstrate that repeated measurement of the static inspiratory PV curve of the respiratory system is well tolerated by the majority of patients with ALI or ARDS. Nonetheless, this maneuver is associated with a small but significant drop in oxygen saturation as well as small but significant increases in HR and mean arterial BP. In addition, we observed a dramatic drop in BP in one patient and in oxygen saturation in another patient during the maneuvers. In two patients, PV curve measurement had to be discontinued: in the first patient, PV curve measurement was discontinued because of an inability to tolerate zero PEEP; in the second patient, PV curve measurement was discontinued because of the development of subcutaneous emphysema. In the latter case, it is unclear whether the subcutaneous emphysema was related to repeated PV curve measurement, or instead to the severity of the underlying illness.

There were no clinical consequences of the physiologic changes induced by PV curve measurement because of careful monitoring and, where appropriate, an immediate response. However, these changes and the need for the procedure to be aborted in two patients highlight the importance of careful monitoring if such maneuvers are performed.

It is also interesting to note that SpO₂ was slightly but significantly increased after PV curve measurement. Although the clinical significance of this

![Figure 3](image1.png)

**Figure 3.** *Top, A:* Triangles represent the difference between the SpO₂ observed immediately after (post) each PV curve measurement and the SpO₂ immediately before (pre) each measurement. Each triangle represents the results of a PV curve measurement in a given patient. *Bottom, B:* Circles represent the difference between the nadir in SpO₂ observed during each PV curve measurement and the SpO₂ immediately before (pre) each measurement. Each circle represents the results of a PV curve measurement in a given patient. Nadir values were available in seven of eleven patients.

![Figure 4](image2.png)

**Figure 4.** Circles represent the difference between the HR observed immediately after PV curve measurement and the HR immediately before each measurement. Each circle represents the results of a PV curve measurement in a given patient. See Figure 3 legend for definition of abbreviations.

![Figure 5](image3.png)

**Figure 5.** Circles represent the difference between the mean arterial BP observed immediately after PV curve measurement and the BP immediately before each measurement. Each circle represents the results of a PV curve measurement in a given patient. See Figure 3 legend for definition of abbreviations.
change is unclear, it is possible that this increase reflects improved recruitment of the lung as a result of the maneuver.22

There are limitations to this study that should be acknowledged. This study was not intended to examine the effect of PV curve determination on formal clinical end points, such as death or duration of intubation. Instead, we sought to determine the immediate impact of PV curve measurement on hemodynamics and oxygenation, changes that may require an immediate response. Our observations have clinical relevance because they highlight the importance of vigilance when conducting these maneuvers.

Although we used a modified super-syringe technique to determine the PV curve, other methods have been described. These include the inspiratory occlusion method, and the more-recently described constant-flow method.23,24 The super-syringe technique has been criticized because it requires the patient to be disconnected from the ventilator. Another drawback is that oxygen uptake in the lungs leads to loss of lung volume, although this artifact is more of a concern when the deflation (rather than the inflation) limb of the PV curve is measured.25,26 The static inspiratory occlusions method does not require disconnection from the ventilator, but requires a large number of occluded breaths and is tedious to obtain.23,27 In contrast, with the constant flow technique, a constant low flow is delivered and a pressure-volume curve is generated.24 In our study, disconnection from the ventilator for the performance of PV curves using the syringe technique was not associated with any adverse events. Ultimately, which of these three techniques should be used is unclear; the super-syringe method was the first to be described and is considered by some to be the reference standard.24 One advantage of this method is that a pneumotachograph is not required, since the volume of each bolus is known. In addition, we believe that using a smaller syringe is preferable to the conventional super-syringe, in that the smaller syringe is easier to manipulate and may allow for a more accurate injection of a predetermined volume of gas.

In this study, we measured the PV curve of the respiratory system as opposed to that of the lung, in keeping with other investigators.5,9 It is important to recognize that in certain patients, such as those with abdominal distention (e.g., ascites), the compliance of the chest wall is decreased, altering the PV curve of the total respiratory system.28 In these circumstances, measuring the PV curve of the lung itself may be more appropriate. In addition, we measured the PV curve of the respiratory system at zero PEEP, which may be different from the PV curve obtained at different levels of PEEP. The measurement of the PV curve at progressive levels of PEEP may be useful in the titration of PEEP.29,30

The significance of the LIP in the static inspiratory PV curve remains controversial. One reason is that the LIP represents only the start of recruitment, and there is ongoing recruitment of lung units as pressure is increased above the LIP; another reason is that tidal ventilation in patients with ARDS may take place on the expiratory limb of the PV curve, not the inspiratory limb.8 It is important to distinguish between recruitment on inspiration, for which the LIP of the inspiratory PV curve may be a helpful guide, and the prevention of derecruitment on expiration, which might be aided by measurement of the expiratory limb of the PV curve.31 We did not measure the expiratory limb of the PV curve in this study, although once the inspiratory PV curve has been measured, the expiratory curve may be measured by aspirating known volumes of gas from the lungs into the syringe and pausing at each point.30

The detection of the LIP and UIP is also somewhat contentious; although some have described substantial interobserver and even intraobserver variability in determining the LIP from a given patient’s PV curve,4 we have found minimal intra-variability and intervariability.11

Finally, the role of PV curve measurement itself in titrating mechanical ventilation remains controversial.32 Its relevance has been called into question by a recent large randomized trial by the ARDS Network; in this study, mechanical ventilation with reduced tidal volumes as opposed to traditional (higher) volumes was associated with a statistically significant 22% reduction in mortality in patients with ARDS.33 In contrast to the trial by Amato et al,9 the PV curve was not measured and PEEP was set according to preset combinations of PEEP and FIO2. Whether setting PEEP according to the PV curve in individual patients would improve outcome any further remains an important yet unanswered question. Nonetheless, our results demonstrate that efforts to answer this question must incorporate careful monitoring of patients during performance of PV curve measurement.

**CONCLUSION**

Frequent PV curve measurement using the super-syringe technique is well tolerated by most patients with ALI/ARDS. In a minority of patients, the maneuver can cause sudden and significant changes in BP, HR, and SpO2. Investigators and clinicians making measurements of PV curves must be alert to these changes and ensure that patients are carefully monitored.
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REFERENCES