Influence of positive airway pressure on the pressure gradient for venous return in humans


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J. ELLINEK, J. KRENN, W. OCZENSKI, F. VEIT, S. SCHWARZ, AND R. D. FITZGERALD. Influence of positive airway pressure on the pressure gradient for venous return in humans. J. Appl. Physiol. 88: 926–932, 2000.—To study the effect of positive airway pressure (Paw) on the pressure gradient for venous return [the difference between mean systemic filling pressure (Pms) and right atrial pressure (Pra)], we investigated 10 patients during general anesthesia for implantation of defibrillator devices. Paw was varied under apnea from 0 to 15 cmH2O, which increased Pra from 7.3 ± 3.1 to 10.0 ± 2.3 mmHg and decreased left ventricular stroke volume by 23 ± 22%. Episodes of ventricular fibrillation, induced for defibrillator testing, were performed during 0- and 15-cmH2O Paw to measure Pms (value of Pra 7.5 s after onset of circulatory arrest). Positive Paw increased Pms from 10.2 ± 3.5 to 12.7 ± 3.2 mmHg, and thus the pressure gradient for venous return (Pms – Pra) remained unchanged. Echocardiography did not reveal signs of vascular collapse of the inferior and superior vena cava due to lung expansion. In conclusion, we demonstrated that positive Paw equally increases Pra and Pms in humans and alters venous return without changes in the pressure gradient (Pms – Pra).

POSITIVE PRESSURE VENTILATION and positive end-expiratory pressure (PEEP) reduce cardiac output in experimental and clinical settings primarily because of a decrease in venous return (3, 15, 21, 23). Total venous return is determined by a driving pressure gradient and the resistance to venous return. According to Guyton’s concept (8, 27), the driving force is the difference between mean systemic filling pressure (Pms), which is the equilibrium pressure in the systemic vessels under the condition of no flow (9), and right atrial pressure (Pra), which is the back pressure to venous return. Because PEEP increases Pra (22), it has been hypothesized that the PEEP-induced reduction in blood flow may result from a decreased pressure gradient (Pms – Pra) (1, 27). However, as suggested at first by Scharf et al. (22) and later demonstrated in experimental studies (5, 19), PEEP also increases Pms, thus preserving the pressure gradient for venous return and buffering the decrease in cardiac output (5, 22). A PEEP-induced decrease in blood flow was, therefore, attributed to an increase in the resistance to venous return (2, 5). Furthermore, a PEEP-induced vascular collapse of the inferior vena cava (IVC) was observed in canine studies (4), consistent with a vascular waterfall (20), causing the back pressure to venous return to be located upstream of the right atrium. In humans, such a vascular collapse of the IVC has been observed by Nakhjavan et al. (18) in hyperinflated patients with emphysema. It is unknown whether this may occur in patients without lung disease during positive-pressure ventilation.

Many clinical studies were conducted to address the change in venous return induced by positive airway pressure (Paw), but virtually no data regarding Pms are available in humans (10). From experimental studies there is concern that PEEP comparably increases Pra and Pms, but this remains hypothetical for humans. The purpose of this study was to measure Pms and to evaluate the changes of the gradient (Pms – Pra) caused by positive Paw in humans. Therefore, we investigated patients undergoing surgical implantation of cardioverter-defibrillator devices under general anesthesia. These devices are designed to automatically detect and terminate life-threatening ventricular tachyarrhythmias by countershock therapy. During the surgical procedure of implantation, ventricular fibrillation is repeatedly induced for threshold testing of the device, resulting in episodes of circulatory arrest long enough to measure Pms (10). Moreover, the study was conducted to address the effect of positive Paw on the dimensions of the great intrathoracic veins, which was studied by echocardiography.

METHODS

Patients and procedure. The study was performed on 14 patients without history of lung disease scheduled for surgical implantation of an implantable cardioverter-defibrillator device (Medtronic, Minneapolis, MN). The protocol was approved by the local ethics committee, and written informed consent was obtained from each patient. An additional nine patients in whom echocardiographic observations were completed are described in Echocardiography. Anesthesia was induced with intravenous midazolam (2 mg), etomidate (0.2 mg/kg), and fentanyl (2 µg/kg). After neuromuscular blockade with vecuronium bromide (0.1 mg/kg), patients were intu-
bated and mechanically ventilated (Cicero, Draeger, Austria) (50% oxygen-50% air, tidal volume 10 ml/kg, respiratory rate 12 breaths/min, PEEP 3 cmH2O). Anesthesia was maintained by propofol infusion (0.4 mg·kg\(^{-1}\)·h\(^{-1}\)) and fentanyl as required. Administration of vecuronium bromide (2 mg) was repeated according to neuromuscular monitoring. After hemodynamic stabilization, lactated Ringer solution was infused at a rate of 200 ml/h throughout the procedure. To optimize oxygen reserve during artificial cardiac arrest, pure oxygen was given 1 min before induction of each episode of ventricular fibrillation until stable hemodynamics were reestablished. After transvenous placement of the endocardial right ventricular defibrillation electrode via the subclavian route, circulatory arrest was induced for defibrillation threshold testing by eight rapid ventricular pacing stimulations followed by a countershock within the T wave, resulting in ventricular fibrillation. From the first rapid ventricular pacing beat, radial artery pressure (Pa) did not show any evidence of effective stroke volume. If the first countershock for threshold testing delivered at least 11 s after induction of circulatory arrest was unsuccessful in terminating ventricular fibrillation, a second internal countershock was applied. If this was unsuccessful, an external rescue shock was delivered. The defibrillation threshold was tested in a step-down procedure with a minimum of two episodes of ventricular fibrillation in each patient.

Physiological monitoring. Paw, Pa, and Pra were simultaneously recorded on a chart recorder (model 2400S, Gould Instruments, Hainault, UK), connected with the transducers (Pressure Monitoring Kit, Baxter-Edwards, Santa Ana, CA) via analog pressure modules (model M1006A T for Pra measurements and model M1006B T for Pa and Paw measurements, Hewlett Packard, Palo Alto, CA). The monitoring devices allowed measurement of Pra with an accuracy of at least 0.5 mmHg. Paw was measured at the proximal end of the endotracheal tube with an air-filled catheter connected with the transducer, balanced at zero level against ambient air. The blood pressure transducers were referenced to the midthorax level. Pa was measured via a cannula in the right or left radial artery (20 gauge, Ohmeda, Swindon, UK) introduced under local anesthesia before induction of general anesthesia. Pra was measured with a catheter (7F, 60 cm, CS-17752, Arrow, Reading, PA) introduced under general anesthesia via the right or left femoral vein. Depending on the patient's height, the catheter was advanced through the common iliac vein into the IVC to a length of 25–35 cm so as to lie with the tip in the right atrium. Transesophageal echocardiography, performed in three patients, verified correct position of the catheter tip as anticipated by physical examination.

To assess changes in venous return, we used the pulse contour method, which takes relative changes in the stroke area under the systolic part of the Pa curve as a measure of relative changes in left ventricular stroke volume (LVSV) (13). This substitution seems justifiable because all measurements were made during apneic conditions. During apnea, venous return equals LVSV, and after a sudden change in Paw a new steady state is reached within seconds (27). Stroke area was determined by averaging the measurements from three consecutive heartbeats during the period from 10 to 15 s of apnea as described in the Experimental protocol.

Experimental protocol. The protocol started 15 min after induction of anesthesia to allow for hemodynamic stabilization. All measurements were done during short apnea. Before implantation of the defibrillator device, the effect of Paw on the intact circulation was tested. Therefore, Pa, Pra, and stroke area were recorded as Paw was varied for 15 s at 0 cmH2O and 15 cmH2O. For 0-cmH2O Paw, patients were disconnected from the ventilator. For 15-cmH2O Paw, inspiratory-hold maneuvers were performed manually under continuous observation of Paw. Subsequent evaluation of the recorded charts revealed reproducible hemodynamic effects. After implantation of the device, in a second step of the protocol the effect of positive Paw on Pms was evaluated. Therefore, episodes of cardiac arrest for threshold testing were performed alternately at 0- and 15-cmH2O Paw. Apnea for circulatory arrest was started 5 s before induction of ventricular fibrillation and was sustained until termination of the arrhythmia, to stable heart action, had occurred. The sequence of Paw levels was varied. The longest apneic period was 32 s with an episode of circulatory arrest of 24 s. All fibrillation episodes were performed for testing the effectiveness of the defibrillator. No additional episode was provoked for study purposes. A representative episode of circulatory arrest is shown in Fig. 1. Data collection was considered successful if Pra taken at 0-cmH2O Paw remained stable throughout the study period within a range of ±0.5 mmHg.

Measurement of Pms. During circulatory arrest, Pms is theoretically measured by taking the value of Pra after equilibration of blood pressures in the arterial and the venous compartment. However, as equilibration is completed, vasomotor reflexes may cause overestimation of Pms. In canine preparations, a duration of circulatory arrest of 5–7.5 s was
appropriate to allow sufficient completion of blood flow and to reach a plateau in Pra before reflex vasoconstriction (5). In our study, we considered Pra to reflect Pms when Pra rose >1 mmHg from 7.5 to 10 s. As observed in canine (5, 16) and human studies (10) of circulatory arrest, Pa significantly exceeds Pra at the time of Pms measurement, indicating that equilibration of blood pressures is incomplete, which may result in underestimation of Pms. Therefore, we corrected our data by considering the ratio of arterial to venous compliance. A given amount of blood that is transferred during cardiac arrest from the arterial to the venous side of the circulation causes a large drop in Pa and a small increase in Pra. The ratio between the change in Pa and Pra reflects the ratio of venous to arterial vascular compliance. Dividing the remaining pressure gradient (Pa − Pra) at the time Pms is taken by the ratio of compliances will, therefore, amount to the value of Pms, which would have further increased if equilibration was complete.

Echocardiography. For clinical reasons, transthoracic echocardiography was only available in three patients undergoing implantation of a defibrillator. To complete our echocardiographic observations, after approval of the ethics committee, we studied consecutively nine additional patients with coronary artery disease before cardiac surgery; four patients with left ventricular ejection fraction >40% and five patients with left ventricular ejection fraction <40%, without history of obstructive lung disease. None of the patients was in acute cardiac congestion, and their Pra matched the Pra of the study group. All patients were in stable sinus rhythm. After induction of anesthesia and hemodynamic stabilization, we performed apneic periods during 0- and 15-cmH2O Paw as described in Experimental protocol. Inspiratory holds for 10–15 s at 25-cmH2O Paw were performed in hemodynamically stable patients with immediate release of Paw if mean Pa decreased below 50 mmHg. During these periods we measured IVC and superior vena caval (SVC) dimensions in long- and short-axes views by two-dimensional transthoracic echocardiography (SONOS 2500, Hewlett Packard). Echocardiographic images were simultaneously recorded on videotape and subsequently analyzed by using the integrated software package. The diameter of the IVC was measured between the point where it crosses the right atrium (3–10 mm distal to the right atrium). The diameter of the SVC was measured between the point where it crosses the right pulmonary artery and the point where it opens into the right atrium (10–15 mm distal to the right atrium). The largest venous dimensions throughout the cardiac cycle, usually occurring during early ventricular diastole, were taken for analysis. Care was taken to observe a maximum length of the intrathoracic veins and any signs of vascular collapse during all phases of the cardiac cycle (narrowing of the proximal part of the SVC during atrial contraction was not considered to reflect compression by the expanding lungs). Because of the small number of observations from the study group, echocardiographic data of those and of the cardiac surgical patients are presented as one group.

Statistical analysis. Data are presented as means ± SD. For statistical analysis, mean values for Pa and Pra were evaluated by planimetric assessment of the recorded strip charts and by averaging the measurements from three consecutive heartbeats during the period from 10 to 15 s of apnea. If minor fluctuations in Pra were present at the time of Pms measurement during circulatory arrest, the mean of Pra from 7 to 7.5 s was taken to reflect mean Pms. If more than one episode of circulatory arrest was performed at one or both Paw levels, data for Pms were averaged. The gradient for venous return was calculated as Pms − Pra for each Paw level. Hemodynamic and echocardiographic data at 0- and 15-cmH2O Paw were compared by using paired t-test. Because no absolute values for LVSV were available from the pulse contour method, data for 15-cmH2O Paw are expressed as relative changes in LVSV, calculated with the stroke area at 0-cmH2O Paw set as 100%. Linear regression analysis was used to test whether relative changes in LVSV were related to changes in the gradient for venous return (Pms − Pra). P < 0.05 was considered statistically significant.

RESULTS

Surgical implantation of the cardioverter-defibrillator device was carried out successfully in all patients, who discharged to a coronary care unit postoperatively within 2 h. Four patients were excluded from analysis: two patients showed variations of Pra >0.5 mmHg because of blood loss and volume replacement. One patient required inotropic support because of hemodynamic instability. In one patient, atrial contractions persisted during the episodes of ventricular fibrillation, causing large a-waves in the Pra curve, making assessment of Pms impossible. Data from 10 patients successfully completing the protocol were taken for statistical analysis. In one of those patients, arrhythmia frustrated assessment of LVSV. In three cases, a second internal countershock was required to defibrillate the heart; no external rescue shock was applied. Demographic data and left ventricular ejection fraction, assessed by radionuclide scintigraphy or ventriculography within 6 wk from the study, are given in Table 1.

During stable hemodynamic conditions before implantation of the defibrillator, increasing Paw from 0 to 15 cmH2O tended to decrease Pa from 70 ± 12 to 66 ± 12 mmHg (P = 0.07), increased Pra from 7.3 ± 3.1 to 10.0 ± 2.3 mmHg (P < 0.001), and decreased LVSV by 23 ± 22% (P = 0.01). After implantation of the defibrillator, during threshold testing we studied a total of 27 episodes of circulatory arrest. Varying Paw during cardiac arrest from 0 cmH2O (n = 14) to 15 cmH2O (n = 13) increased Pms from 10.2 ± 3.5 to 12.7 ± 3.2 mmHg (P < 0.001). Thus the calculated pressure gradient for venous return (Pms − Pra) remained unaffected by

Table 1. Demographic data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
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<th>Diagnosis</th>
<th>LVEF, %</th>
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<tr>
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<td>CAD</td>
<td>35</td>
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<tr>
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<td>DCMP</td>
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<td>M</td>
<td>CAD</td>
<td>18</td>
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<td>CAD, ACBG</td>
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<td>AVR</td>
<td>40</td>
</tr>
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<td>59</td>
<td>M</td>
<td>CAD, ACBG</td>
<td>22</td>
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<tr>
<td>9</td>
<td>58</td>
<td>M</td>
<td>DCMP</td>
<td>15</td>
</tr>
</tbody>
</table>

M, male; F, female; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; DCMP, dilated cardiomyopathy; ACBG, aortocoronary bypass grafting, previously undergone; CMP, cardiomyopathy; AVR, aortic valve replacement, previously undergone.
positive Paw \( (2.9 \pm 1.3 \text{ vs. } 2.7 \pm 1.3 \text{ mmHg for 0- and 15-cmH}_2\text{O Paw, respectively; } P = 0.40, \text{ Fig. 2}). \) In individual patients, Paw-induced relative changes in LVSV were not correlated with changes in the gradient for venous return \( (n = 9; \ P = 0.74) \) or left ventricular ejection fraction (Fig. 3).

The pressure gradient between Pa and Pra at the time Pms was measured was \( 20 \pm 7 \text{ mmHg at 0-cmH}_2\text{O Paw and } 18 \pm 4 \text{ mmHg at 15-cmH}_2\text{O Paw. The ratio of arterial to venous compliance (calculated as the ratio between the increase of Pra and the decrease of Pa during 7.5 s of circulatory arrest) was 1.17 at 0-cmH}_2\text{O Paw and 1.18 at 15-cmH}_2\text{O Paw. Therefore, transfer of volumes sufficient to lower Pa to Pms would have raised Pms by } \frac{1}{17} \text{ (at 0-cmH}_2\text{O Paw) and } \frac{1}{18} \text{ (at 15-cmH}_2\text{O Paw) of that remaining pressure gradient. Therefore, correction of Pms data for incomplete equilibration of blood pressures increased Pms at both Paw levels by a mean of 1.2 mmHg to 11.4 \pm 3.6 \text{ mmHg during 0-cmH}_2\text{O Paw and to } 13.9 \pm 3.4 \text{ mmHg during 15-cmH}_2\text{O Paw. Increasing Paw did not change the calculated pressure gradient (corrected Pms – Pra) for venous return (4.1 \pm 1.4 \text{ vs. } 3.9 \pm 1.6 \text{ mmHg for 0- and 15-cmH}_2\text{O Paw, respectively; } P = 0.43).} \)

Echocardiography in a total of 12 patients enabled us to visualize the entire intrathoracic IVC down to a region distal to the junction of hepatic veins. The SVC was imaged for a length of 3.5–5 cm up to a region cranial to the crossing of the right pulmonary artery. Increasing Paw from 0 to 15 cmH\textsubscript{2}O did not change the IVC diameter \( (22.5 \pm 3.8 \text{ vs. } 21.8 \pm 3.7 \text{ mm; } P = 0.14) \) but significantly reduced the SVC diameter \( (18.2 \pm 1.6 \text{ vs. } 14.8 \pm 2.6 \text{ mm; } P < 0.001). \) Changes in the SVC diameter were inversely correlated with Pra \( (P < 0.05). \) No signs of venous collapse were observed due to compression by the expanding lungs under study protocol conditions. However, marked narrowing of the SVC to \(<5 \text{ mm in diameter (according to a reduction in the cross-sectional area by } >90\% \text{) was observed in two patients with 25-cmH\textsubscript{2}O Paw, whereas IVC diameter was only slightly reduced at this Paw level.}

**DISCUSSION**

The measurement of Pms under clinical conditions is limited by the availability of planned, unavoidable circulatory arrests. During surgical implantation of cardioverter-defibrillator devices, we found a clinical setting meeting this requirement. Most values for Pms derived from our patients were within the range reported in animal studies \( (5, 6, 19, 27). \) Patients with Pms values exceeding this range were, even without clinical signs of decompensated congestive heart failure, in end-stage heart disease. With our study in humans, we demonstrated that positive Paw of 15 cmH\textsubscript{2}O increased Pms and Pra equally. As a consequence, the pressure gradient for venous return \( (\text{Pms} – \text{Pra}) \) remained unaffected by positive Paw, thus confirming the findings of several animal studies \( (5, 19, 22). \) Positive Paw decreased LVSV even in the absence of changes in the pressure gradient for venous return.

Measurement of Pms during cardiac arrest is based on the assumption that complete equilibration of blood pressures had occurred at the moment Pms is recorded. Starr and Rawson \( (24)\) reported static blood pressures from postmortem studies in patients with and without cardiac congestion of 21 and 9 cmH\textsubscript{2}O (mean values), respectively. Clinical assessment of Pms requires short episodes of cardiac arrest. Baroreflex activation may occur after seconds and results in overestimation of Pms. Although some changes in vascular tone may be seen within the short time frame studied, it is unlikely that this had major effects on our data because baroreflexes are blunted under anesthesia \( (7)\), and from 7.5 to 10 s from the onset of circulatory arrest the rise of Pra never exceeded 0.5 mmHg. On the contrary, early measurements during circulatory arrest may underestimate Pms because of incomplete equilibration of blood flow. To provide rapid equilibration of blood flow...
pressures for Pms measurement, pumping blood from the aorta into the great veins has been recommended by Guyton et al. (9). However, comparable values for Pms were derived without arterial-venous pumps (7), and, more recently, Pms was determined in a canine study after 5–7.5 s of cardiac arrest (5).

At the time of our Pms measurements, 7.5 s after the onset of circulatory arrest, Pa still significantly exceeded Pra. The pressure gradient persisted even after prolonged episodes of circulatory arrest up to 24 s and is most likely due to a Starling resistor mechanism (i.e., vascular waterfall) in the precapillary vascular bed (16). Such a waterfall effect will prolong the time blood flow requires to equilibrate blood pressures and might cause underestimation of Pms. We corrected our Pms data by dividing the remaining pressure gradient by the ratio of venous to arterial vascular compliance. This method is based on the assumption that, during circulatory arrest, a given blood volume is released from the arterial system and added into the venous vasculature, causing pressure changes according to the vascular compliances. However, this is a simplified model of tissue blood flow. If arterial inflow is stopped abruptly, venous outflow may continue distal to the Starling resistor (16), making changes in arterial and venous pressures independent of the ratio of their compliances. However, our method should be accurate enough to assess the dimension of underestimation of Pms due to incomplete equilibration of pressures. Mean underestimation of Pms was 1.2 mmHg at both Paw levels, which is a small value but represents ~30% of the observed pressure gradient for venous return. Fessler et al. (5) observed a mean pressure gradient for venous return of 3.89 ± 0.26 (SE) mmHg under control conditions without PEEP, which is comparable to the 4.1 ± 1.4 mmHg gradient observed by us.

During PEEP ventilation, reflex vasoconstriction increases Pms (5, 9), which is important to counterbalance the decrease in cardiac output (5). However, even after denervation of peripheral baroreceptors and during total spinal anesthesia, PEEP-induced increases in Pms are observed (5). In our study, measurements were made during 15-s periods of positive Paw, thus avoiding profound vasoreflex activation. Therefore, our data during positive Paw may reflect the hemodynamic effect of a prolonged mechanical inspiration rather than the circulatory effect of PEEP. This may account for the relatively small increase in Pms (and also Pra) induced by 15-cmH₂O Paw in our study (2.5 ± 0.6 mmHg), compared with experimental studies reporting an increase in Pms by ~4 mmHg (data only presented as figure in Ref. 5) under 15-cmH₂O PEEP (5) and by 3.4 mmHg under 10-cmH₂O PEEP (19). This problem could have been avoided by ventilating our patients with 15-cmH₂O PEEP for several minutes and to pause at end expiration when they were fibrillated. However, defibrillator devices are implanted in patients with severe heart disease, and threshold testing is, irrespective of its low mortality, a potentially life-threatening procedure. Ventilation with PEEP would profoundly reduce cardiac output for minutes and would, therefore, reduce the patients’ metabolic reserves for subsequent prolonged episodes of circulatory arrest if defibrillation were unsuccessful. For ethical reasons, we refused a study design that would expose patients to an increased risk. Finally, because cardioverter-defibrillator devices are increasingly implanted without the use of general anesthesia (25), it seems questionable to prolong general anesthesia because of study purposes in this high-risk population.

A reduction in blood flow induced by PEEP (5, 19) and short increases in Paw (our data) without a decreased driving pressure gradient (Pms − Pra) indicates an increase in the resistance to venous return (5). Furthermore, an increase in lung volume may create vascular waterfalls (20) at the diaphragmatic inlet of the IVC. In canine studies, PEEP increased the critical downstream pressure of the IVC and SVC, below which venous return was maximal (6), suggesting that the condition of a vascular waterfall would occur when the pressure within a great intrathoracic vein was below this critical pressure. In the presence of such a waterfall, the effective back pressure to venous return would be higher than Pra and located upstream of the right atrium, thus making changes in venous return independent from changes in Pra. Such a vascular collapse of the IVC has been demonstrated in dogs, especially in the left lateral position (4). In this species a substantial part of the IVC is located cephalad of the diaphragm within the thorax. Thus the expanding lungs may directly compress the IVC, causing vascular collapse. By contrast, in humans the IVC commonly opens into the right atrium immediately at the thoracic inlet. In a study in critically ill patients under mechanical ventilation with PEEP up to 10 cmH₂O and mean positive Paw up to 22 cmH₂O, blood pressures in the common iliac vein and the SVC were found to be interchangeable (11). In another study, Jardin et al. (14) measured IVC diameter distal to the junction of the hepatic vein in healthy volunteers. During spontaneous inspiration, which enhanced venous return to the right heart, they observed a decrease in vena caval diameter. During continuous positive Paw breathing at 15 cmH₂O the IVC diameter was increased, consistent with a reduction in venous return, but the percent inspiratory decrease of vena caval diameter was unchanged (14). The presence of a vascular waterfall between the IVC and the right atrium should have altered the inspiratory change of caval diameter. In our study, no evidence of intrathoracic venous collapse under study protocol conditions was found by using transesophageal echocardiography. The IVC dimensions were especially unaffected by inspiratory-hold maneuvers. By contrast, inspiratory hold significantly reduced the SVC diameter. This finding was associated with low Pra, but signs of vascular collapse were definitely not seen during 15-cmH₂O Paw. Therefore, a PEEP-induced vascular waterfall creating important pressure gradients within the great veins should not be a common phenomenon in humans. However, Nakhjavan et al. (18) observed a pressure gradient within the IVC during spontaneous inspiration in patients with emphy-
semi. Abnormal caval blood flow was attributed to severe hyperinflation of the lungs with a depressed diaphragm, thus exposing parts of the IVC to the lungs. In our study we observed subtotal compression of the SVC in two patients at 25-cmH2O Paw. Thus, in humans, positive-pressure ventilation could create a vascular waterfall in the SVC, but this may be restricted to peak inspiratory pressure and low central venous pressure.

Because mechanical inspiration changes abdominal pressure, which has important implications for splanchic and nonsplanchic IVC blood flow, our data have to be discussed with respect to the concept of abdominal vascular zone conditions (26). Even without measurement of abdominal pressure, we suggest that our patients started in a physiological abdominal vascular zone 3 condition at baseline, in which IVC pressure exceeds abdominal pressure and vascular waterfalls are absent. If the respiratory muscles are paralyzed, which was the case in our study, any positive inspiratory pressure must overcome the elastance of the lung and the diaphragm before transmitting the remaining force to the abdomen. The increase in abdominal pressure will therefore be less than the increase in pleural pressure. It is unlikely that mechanical inspiration may change zone 3 into zone 2 conditions because this would require an increase in abdominal pressure that exceeds the increase in IVC pressure. Therefore, based on the lack of compression of the IVC from our observations, we suggest that zone 3 conditions were still present during 15-cmH2O Paw and that mechanical inspiration significantly affected transhepatic resistance to venous flow. This is supported by experimental findings from Brienza et al. (2), who demonstrated that PEEP, besides an increase in the back pressure to flow, affects splanchic flow because of an increase in liver venous resistance, resulting from direct mechanical compression of the liver by diaphragmatic descent. However, in patients with increased abdominal pressure and a zone 2 abdomen at baseline (i.e., vascular waterfall at the diaphragm), the findings of our study would be expected to be different.

A limitation of our study was the substitution of the measurement of venous return, which was impossible in the clinical setting, by the measurement of LVSV using the pulse contour method. Cardiac output measurement by thermodilution was not possible because a pulmonary artery catheter could potentially interfere with the implanted right heart endocardial defibrillation electrode. However, after an acute increase in Paw, a change in venous return is transmitted to the aorta within a few heartbeats, and a new hemodynamic steady state is reached within seconds (12, 27). Changes in LVSV should, therefore, adequately reflect changes in venous return during a quasi-steady-state condition after 10–15 s of inspiratory hold. Although the pulse contour method permits adequate estimation of LVSV (13), it is not generally accepted because it requires constant downstream resistance and compliance over the time period studied. In our patients, the inspiratory hold maneuvers resulted in a wide range of hemodynamic response, which may be the range of ventricular function. However, no relationship was found between baseline ventricular function as measured by ejection fraction and the cardiovascular effect of positive Paw. The observed range of hemodynamic response may further result from our study design because we controlled Paw and not lung volume. Differences in lung compliance may, therefore, add to the individual response to increased Paw, even in subjects without history of lung disease (17).

Transfemoral placement of the central venous catheter for measuring Pra was chosen to avoid any interference with the surgeon’s subclavian approach. Correct placement of the catheter tip proximal to the right atrium was verified by echocardiography in three patients. The absence of venous collapse as assessed by our echocardiographic studies and the absence of a pressure gradient between the SVC and the common iliac vein in mechanically ventilated patients (11) make it unlikely that small variations of the catheter position in the other patients would have influenced our Pra data.

In conclusion, we measured Pra in humans and confirmed values obtained in animal experiments. We demonstrated that an acute increase of Paw from 0 to 15 cmH2O increased Pra comparable to the rise in Pra. Changes in venous return occurred independent of changes in the pressure gradient for venous return calculated as (Pms − Pra). Vascular collapse of great intrathoracic veins, which is a common finding in canine studies, was not observed under those conditions.

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