Effect of positive pressure on venous return in volume-loaded cardiac surgical patients

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Van den Berg, Paul C. M., Jos R. C. Jansen, and Michael R. Pinsky. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. J Appl Physiol 92: 1223–1231, 2002. First published November 23, 2001; 10.1152/japplphysiol.00487.2001.—The hemodynamic effects of increases in airway pressure (Paw) are related in part to Paw-induced increases in right atrial pressure (Pra), the downstream pressure for venous return, thus decreasing the pressure gradient for venous return. However, numerous animal and clinical studies have shown that venous return is often sustained during ventilation with positive end-expiratory pressure (PEEP). Potentially, PEEP-induced diaphragmatic descent increases abdominal pressure (Pabd). We hypothesized that an increase in Paw induced by PEEP would minimally alter venous return because the associated increase in Pra would be partially offset by a concomitant increase in Pabd. Thus we studied the acute effects of graded increases of Paw on Pra, Pabd, and cardiac output by application of inspiratory-hold maneuvers in sedated and paralyzed humans. Forty-two patients were studied in the intensive care unit after coronary artery bypass surgery during hemodynamically stable, fluid-resuscitated conditions. Paw was progressively increased in steps of 2 to 4 cmH2O from 0 to 20 cmH2O in sequential 25-s inspiratory-hold maneuvers. Right ventricular (RV) cardiac output (COtd) and RV ejection fraction (EFrv) were measured at 5 s into the inspiratory-hold maneuver by the thermodilution technique. RV end-diastolic volume and stroke volume were calculated from EFrv and COtd was 0.05

The rate of venous return is proportional to the ratio of the pressure gradient between the peripheral vascular reservoirs and Pra and to the resistance to venous return (6, 8, 9). The pressure in the peripheral vascular reservoirs is referred to as mean systemic filling pressure (Pms) and is analogous to the systemic vascular stop-flow pressure. On the basis of this model, increases in Paw reduce cardiac output by selectively increasing Pra, whereas both Pms and resistance to venous return remain constant. Using this construct, we (24) and others (32) used dynamic changes in RV outflow to Pra relations during IPPV to construct in-

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instantaneous venous return curves in animal models. These studies demonstrated that the calculated Pms values from the instantaneous venous return curves closely reflected directly measured stop-flow Pms. However, other animal studies (27, 31) suggest that the relation between diaphragmatic descent, intra-abdominal pressure (Pabd), and venous return may be more complex than that described above. As lung volume increases, diaphragmatic descent will increase (Pabd) and, in addition, will indirectly increase Pms by compression of the liver. The interactions between changes in Pra, Pms, and the resistance to venous return in humans during IPPV are not well characterized.

Considering the potential clinical relevance of these interactions, we studied the effects of increasing Paw on Pra, Pabd, and venous return in humans. We evaluated quasi-steady-state effects on venous return of brief inspiratory-hold maneuvers (CPAP) in sedated, fluid-filled, postoperative cardiac surgery patients. To maximize any potential effects of Pabd on Pms, we studied these subjects only after they became hemodynamically stable, which usually meant after an interval of intravascular fluid resuscitation to restore their effective circulating blood volume. We hypothesized that increases in Paw induced by a passive inspiratory-hold maneuver would minimally alter venous return because the increases in Pra would be offset by concomitant increases in Pabd.

METHODS

Fifty-four postoperative cardiac surgery patients were selected for the study within a period of 6 mo. The study was approved by the ethical committees for human experimentation of both university hospitals, and all patients gave informed consent. No complications occurred as a result of the study. All subjects underwent uncomplicated coronary artery bypass grafting (CABG), were functionally and clinically free of congestive heart failure, and had a normal preoperative contraction pattern on left ventriculography. None had more than mild obstructive pulmonary disease (forced expiratory volume in 1 s >75% of expired vital capacity). None of the subjects was receiving 3-adrenergic-blocking agents at the time of the study. Excluded from the study were subjects with left ventricular (LV) end-diastolic pressure above 15 mmHg, LV ejection fraction below 50%, atrioventricular conduction defects, arrhythmias, unstable angina pectoris, heart failure, or preoperative diagnosis of myocardial infarction.

In 12 of the selected patients, the results of the experiments could not be used for further analysis. In six of these subjects, the hemodynamic variables could only be kept within 10% of the preexperiment values by therapeutic interventions that interfered with our measurements, i.e., start or change of dosage of inotropic and vasodilating agents. In none of these subjects could the deterioration of their hemodynamic status be ascribed to the protocol maneuver. In three subjects, there were technical reasons for excluding the data from further analysis, as indicated by the error diagnostics of the Baxter REF1 computer. In two of these subjects, the pulmonary artery catheter pressure readings showed a damped pulmonary arterial pressure (Ppa) signal, and in one of these subjects the tip of the pulmonary artery catheter was located in West zone I conditions (19). In this position, the pulmonary artery occlusion pressure (Ppao) curve did not show typical a, c, and v waves but rather tracked Paw. In another three subjects, severe arrhythmias, characterized by supraventricular and atrial fibrillation, precluded the accurate measurement of cardiac output by thermodilution (COtd) and RV end-diastolic volume (EDV). All data of these patients were excluded to prevent unreliable fits of the relation of Pra vs. cardiac output on the basis of insufficient data. Thus 42 of the patients, 35 men and 7 women, were used as subjects for the analysis of the hemodynamic response to increased Paw. Their mean age was 59 yr (range 40–74 yr), their mean height was 174 cm (range 159–188 cm), and their mean weight was 78 kg (range 52–110 kg), and these subjects had on average 4 CABG (range 1–6 CABG).

Hemodynamic measurements. All the patients were instrumented with arterial and pulmonary artery catheters before the start of the surgical procedure. A standard lead II electrocardiogram was used to monitor heart rate. The airway pressure was measured at the entrance of the endotracheal tube and was used to represent Paw. Systemic blood pressure was measured through a fluid-filled 7-Fr radial artery catheter. Pra, Ppa, and Ppao were measured through a pulmonary artery thermocatheter model 7.5-Fr rapid-response thermocatheter model 93A-431H (Baxter-Edwards, Santa Ana, CA). All pressure transducers were referenced to the midaxillary level and connected to pressure transducers (model 1290C, Hewlett-Packard, Palo Alto CA). RV COtd, RV ejection fraction (EFrv), RV stroke volume, RV end-systolic volume (ESV), and RV EDV were measured by the thermodilution technique by using 10-ml aliquots of 5% dextrose in water (REF-1 Ejection Fraction/Cardiac Output Computer, Baxter-Edwards). Care was taken to keep the temperature of the 10-ml 5% dextrose in water injectate between 8 and 12°C with the use of an injectate delivery system (CO-set II model 93–500, Baxter-Edwards). Reproducibility of the COtd and EFrv measurements was aided by electronic triggering the mechanical injection of the cold bolus to the T wave of the electrocardiogram (23). If an arrhythmia occurred during the measurements, the results were discarded and measurements were repeated. Pabd was measured via a side port of the urinary bladder catheter as described by Kastan et al. (16) and validated by others (11, 23).
12). During the experiments, the connection with the urinary reservoir was blocked.

All patients were receiving controlled mechanical ventilation with a tidal volume of 12 ml/kg at a respiratory rate of 12 breaths/min and an inspired O2 fraction of >0.21. Before the start of the protocol, arterial blood gases were collected anaerobically and measured (model ABL-3, Radiometer, Copenhagen, Denmark). Ventilator settings were adjusted as needed to maintain an arterial O2 saturation (Sao2) >96% and an arterial PCO2 between 35 and 45 Torr. To prevent a cold-induced reflux of the airways, care was taken to keep the temperature of inflated O2 at 34°C (13, 28). At the same time, this prevented a drift of the baseline temperature of the pulmonary artery, where the fast response thermostir of the pulmonary artery catheter was located (15). Sao2 was continuously measured with a pulse oxymeter (Nelcor), and end-tidal CO2 levels were checked with a capnograph (Hewlett-Packard, Palo Alto, CA). During all experiments, Sao2 did not change and the end-expiratory CO2 was stable within ±2%.

Protocol. Patients were anesthetized with high-dose fentanyl (50 μg/kg). This anesthetic technique with addition of dopamine doses <5 μg·kg⁻¹·min⁻¹ and nitroglycerine doses <0.5 μg·kg⁻¹·min⁻¹ was used because of its stabilizing effects on the cardiovascular system during both the intra- and postoperative intervals (6). Postoperative midodranol (2—4 μg·kg⁻¹·min⁻¹) and morfine (2 μg·kg⁻¹·min⁻¹) were added. After the coronary bypass operation, all patients were transported to the intensive care unit, and, after a stabilization period of at least 2 h and at maximum 5 h, a baseline hemodynamic analysis was performed. At that moment all hemodynamic variables (Pra, Ppa, Ppao, COtd, EFrv, heart rate, and systemic blood pressure) had to be within 10% of the therapeutic goals determined by the operating team; otherwise, the patient was not included in the study. The experiments were started when the central body temperature was at least 37°C. During the experiments, all subjects were still under the sedative effects of fentanyl given during the operation.
The protocol consisted of repeated inspiratory-hold maneuvers of 25-s duration. These inspiratory-hold maneuvers were separated by 3-min intervals to regain the same hemodynamic steady state as before the first inspiratory hold. Resumption of a stable baseline was documented by restoration of all measured hemodynamic variables to within 10% of their initial baseline values. Then the next maneuver was performed, with an inflation volume 250 ml greater than during the previous maneuver. In this way, a series of maneuvers resulted in a stepwise increase in both Paw and lung volume. During the first two duplicate inspiratory-hold maneuvers, no gas was inflated in the lungs and the resultant Paw equaled ambient pressure. The hemodynamic measurements performed during these maneuvers were used to derive the baseline values of all variables against which changes induced by increased Paw were compared. Lung inflation was performed with the same inspired O2 fraction used to ventilate the subject.

Each individual inflation challenge was divided into four phases as described in Fig. 1. Phase I started at end expiration and represents the pre-inflation period. In this period, the electronic sampling of data was started. Data sampled during this period were used to evaluate the hemodynamic status of the subject and to evaluate whether hemodynamic deterioration outside the 10% range, as described in the protocol, had taken place. During phase II, an extra volume of gas was inflated in the lungs and created a peak pressure in the trachea. This peak in pressure is the result of resistance in the airways. After this peak pressure, phase III started at the moment a plateau in Paw had been reached. The inflated volume, the functional residual capacity, and the compliance of the lungs and chest wall determine plateau Paw. The maximal plateau Paw we
strove for was 20 cmH2O. Phase IV describes the period in which Paw was allowed to return to its preinspiratory pressure by passive exhalation of the extra volume from the lungs. The effect of an increase in Paw was evaluated at plateau Paw. In practice, all data used for further analysis were derived 5–6 s after lung inflation was started.

A delay interval of >1 min between consecutive inspiratory-hold maneuvers was chosen because the time constant of volume shifts between the thoracic, abdominal, and peripheral compartments of the circulation is within the order of 1 min (7). Between the inspiratory-hold maneuvers, the hemodynamic status of the subject was controlled with fluid infusions as required by monitoring Pra (RV filling pressure) and Ppao. In this way, subjects were kept in a hemodynamic steady state throughout the protocol. In all patients, the total infusion rate of fluids during the protocol was <100 ml/h.

Data from three of the subjects were discarded because of inaccurate pressure measurements.

All trials of increased Paw with a specific inflation volume were repeated in duplicate. Data were discarded if the thermodilution profile demonstrated irregularities in its waveform. On the basis of this RV volume, calculations were discarded in three subjects. A trial of increased Paw was repeated until acceptable duplicate measurements were within 10% of each other. It was never necessary to perform more than four measurements per level of lung inflation.

A randomly selected group of six subjects were also studied by transesophageal echocardiography for tricuspid insufficiency at 0 and 20 cmH2O of Paw to evaluate whether such increases in Paw resulted in a pressure-dependent increase in tricuspid valve insufficiency. In none of these subjects could a Paw-dependent tricuspid valve insufficiency be detected. As a standard measure in all 42 subjects, the Pra waveform was also evaluated to detect tricuspid valve insufficiency. In none of the subjects was a pressure-dependent tricuspid valve insufficiency noticed, by using this criterion.

Data analysis. All data were digitized with a sample frequency of 100 Hz, converted with a 12-bit resolution, and stored on hard disk for later evaluation. Sampling of data started just before the beginning of an inspiratory hold and was stopped 4 s after termination of the strain phase of the maneuver.

The thermodilution curve was recorded in phase III, 5 s after Paw had been increased. The temperature curve was checked as to whether the descending limb of the temperature had an exponential decay and returned to its baseline value. If this was the case, then the measurements were used for further analysis; otherwise, the measurements were discarded and the trial was repeated.

The analysis of the data was concentrated on the changes of the hemodynamic variables induced by the increase in Paw. Linear regression analysis was performed, by using the method of least squares. Analyses of the Paw effects on the measured hemodynamic variables were performed with repeated-measures analysis of variance by using a post hoc Student-Neuman-Keuls test (BMDP-V statistical package, Berkeley, CA). Statistical significance reports differences corresponding to a P < 0.05 unless otherwise stated. Data are presented as means ± SD.

RESULTS

The hemodynamic status of the 42 subjects included in the study is shown in Table 1, and an example of the effects of an inspiratory-hold maneuver on the measured variables is shown in Fig. 2. Increases in lung volume increased Paw. An example of the relationship between the inflated lung volume and Paw is given in Fig. 3.

Per subject, a mean of 7 ± 2 duplicate inflations of the lungs at increasing inflation volumes could be performed before Paw increased to −20 cmH2O in phase III.

The Paw created during the range of inflation volumes varied from 0 to 19.01 ± 2.7 cmH2O.

The maximal inflated volume inflated per subject was on average 1,750 ml (range 1,250–2,250 ml). As expected, total compliance, i.e., lung plus thorax, was normal (mean 85 ml/cmH2O, range 62–112 ml/cmH2O).

Increasing Paw in this fashion also increased Pra. However, only 32 ± 20% of the increase in Paw was represented in the increase in Pra. An example of the relationship between Pra and Paw for one subject as Paw was progressively increased is shown in Fig. 4A. The ratio of change (Δ) in Paw to ΔPra as determined by the slope of the linear regression line of all Paw vs. Pra data points for individual subjects is shown in Fig.
for the complete data sets. Each point represents the amount of pressure transmitted from the proximal airway to the right atrium. A value of 0 means that no pressure is transmitted from the proximal airway to the right atrium as \( \text{Paw} \) was progressively increased, whereas a value of 1 means that all the pressure applied to the airways is transmitted to the right atrium. Although increasing \( \text{Paw} \) always increased Pra, most data cluster around a mean of 0.32. Further evaluation of this relationship by using a polynomial function did not improve the regression fit or alter the proportion of increased \( \text{Paw} \) seen in Pra. In an attempt to maximize the potential effect of \( \text{Paw} \) on Pra, we measured the maximal \( \Delta \text{Pra} \) as \( \text{Paw} \) was increased from 0 to its final pressure of \( \sim 20 \text{ cmH}_2\text{O} \). The resultant Pra values ranged from \( 8.12 \pm 3.4 \text{ mmHg} \) at 0 \( \text{Paw} \) to \( 15.42 \pm 3.0 \text{ mmHg} \) at maximal \( \text{Paw} \). The mean Pra-to-Paw ratio was \( 0.32 \pm 0.2 \), which was the same as when all data pairs were included in the analysis.

Inflation of the lungs also altered \( \text{CO}_{td} \). The relation between \( \text{CO}_{td} \) and Pra as Pra is varied is commonly referred to as the venous return curve (9). An example of such venous return curves for six subjects is shown in Fig. 5. On average, each experiment consisted of a series of 14 inflation maneuvers giving 14 data pairs for the relationship of \( \text{CO}_{td} \) to Pra. Linear regression analysis on these pooled data per subject resulted in a slope, \( \text{CO}_{td}/\text{Pra} \). Classically, \( \text{CO}_{td}/\text{Pra} \) produces a negative slope over this range of Pra values, has described previously (9). Thus \( \text{CO}_{td}/\text{Pra} \) usually decreases as Pra increases because of an increase in \( \text{Paw} \). A positive \( \text{CO}_{td}/\text{Pra} \) slope would mean that \( \text{CO}_{td} \) increases with...
an increase in Pra. The $\Delta CO_{td}$ vs. $\Delta Pra$ for group was $0.05 \pm 0.15$ l·min$^{-1}$·mmHg, which is not significantly different from a $\Delta CO_{td}$ of 0 (Fig. 6). Heart rate did not change during the maneuver (maximal change $-4.9 \pm 9\%$ from 0 to 20 cmH$_2$O Paw).

We believe that the apparent nonphysiological $CO_{td}$/Pra relation during sustained positive-pressure inspiratory-hold maneuvers can be explained by the increased Paw and lung volume associated with an increase in Pabd. The group $\Delta$Pabd/$\Delta$Paw was $0.20 \pm 0.1$, meaning that $\sim 20\%$ of the increase in Paw was reflected in an increase in Pabd. Although this increase is relatively small, it is of the same magnitude of the transmission of Paw to Pra. In fact, the $\Delta$Pabd relative to the $\Delta$Pra was $0.73 \pm 0.36$, which is not significantly different from unity. Thus 70% or more of the increased Pra is also reflected in an increase in Pabd. The increase in Paw and lung volume also resulted in a slight but significant increases in RV EDV of 18.3 $\pm$ 24% at 20 cmH$_2$O Paw.

**DISCUSSION**

Our study demonstrates that the application of up to 20 cmH$_2$O CPAP in hemodynamically stable postoperative cardiac surgery patients is associated with minimal short-term changes in RV output despite an associated increase in Pra. Thus changes in systemic venous return during CPAP are not solely influenced by increases in Pra. The data further suggest that a predominant mechanism responsible for the maintenance in venous return during CPAP is the associated increase in Pabd that will indirectly increase Pms. Our findings are consonant with those described by Wise et al. (34) and Fessler et al. (5), who measured venous return in highly instrumented canine models. Our data are in contrast, however, with porcine data reported by Versprille and Jansen (32), who showed that CPAP-induced increases in Pra induced proportional decreases in RV output. Although venous return varied considerably between subjects in our study, in almost none of the patients could an estimate of Pms be made from our data on the basis of the model of Guyton (8, 9).

According to the theory proposed by Guyton et al. (8, 9), an isolated increase in Pra will decrease systemic venous return by decreasing the pressure gradient for venous blood flow, which is defined as the different between Pra and Pms and is inversely proportional to the resistance to venous return. Using this concept, Pinsky (24) constructed “instantaneous” venous return curves in instrumented dogs by plotting Pra to RV stroke volume during both IPPV inspiration with small tidal volumes and passive Valsalva maneuvers. A linear regression line could be fitted through their Pra-RV stroke volume data pairs. The extrapolated zero stroke volume intercept point, referred to as instantaneous Pms, correlated significantly ($r = 0.90, P < 0.001$) with Pms measured during no flow. Versprille and Jansen (32) further demonstrated a high correlation between inspiratory-hold maneuver-induced Pra and RV stroke volume changes in eleven 8- to 10-wk-old Yorkshire pigs. The total compliance of these pigs ($\sim 1$ ml·kg$^{-1}$·cmH$_2$O$^{-1}$) is comparable to the compliance of the patients included in our study (85 ml·cmH$_2$O$^{-1}$·78 kg$^{-1}$ = 1.1 ml·kg$^{-1}$·cmH$_2$O$^{-1}$). The Versprille and Jansen methodology of making measurements during the plateau phase of a series of increasing Paw inspiratory-hold maneuvers is in many respects comparable to the method used in our protocol. However, they measured RV stroke volume using a pulmonary arterial flow probe in normovolemic animals. Furthermore, they used inspiratory volumes up to 30 ml/kg after closing the thorax and restoring the intra-thoracic pressure to normal values, whereas we were limited to inspiratory volume up to 1,250 ml/78 kg (= 16 ml/kg) in patients with a thorax drain.

We measured CO$_{td}$ in fluid-filled, probably hypervolemic, patients. By what mechanisms can venous return be sustained despite an increase in downstream pressure? Venous return can be maintained as Pra increases, if Pms increases by the same amount, such that the pressure gradient for venous return does not change, or if the resistance to venous return decreases to offset a decrease in driving pressure. When Pra is increased by IPPV, an associated increase in Pms is likely because of the obligatory increase in Pabd or direct compression of the liver induced by diaphragmatic descent (22, 31) and by squeezing of the lungs (33). Although recognized, the transmission of Paw to the abdominal space has been ignored in most hemodynamic studies of heart-lung interactions (24, 32). Our data demonstrate that not only does CPAP in-
crease Pabd but also over 70% of the increase in Pra is realized with an associated increase in Pabd. Because a large proportion of the venous reservoirs are directly influenced by Pabd (22), these data suggest that the driving pressure for venous return is not reduced during IPPV by as much as would be predicted if Pra had been increased in an isolated fashion.

The fact that Pra increased more than Pabd despite no change in venous return in the majority of patients suggests that either the changes in driving pressures were too small to affect the rate of venous return or that the resistance to venous return also decreased. If inferior vena caval flow were to increase during inspiration due to a redistribution of venous drainage away from the portal circuit to the systemic venous circuit, a situation described in both animals (31) and humans (22), then the resistance to venous return should also decrease. Increases in Pabd will increase cardiac output. Matuschak et al. (20, 21) examined further the effects of PEEP and the timing of increased Paw on both hepatic outflow and intrahepatic resistance. Their collective data suggest that hepatic compression by the descending diaphragm could induce an inspiratory increase in hepatic venous outflow. This inspiration-induced augmentation in flow may combine with the increase in Pabd to sustain venous return constant during transient inspiratory-hold maneuvers.

Our hemodynamic data are also internally consistent. Neither EFrv nor RV EDV changed from 5 to 6 s after CPAP. If anything, RV EDV increased slightly as Paw increased. Several workers have assumed that any increase in RV EDV during lung inflation is the result of an increase in pulmonary vascular resistance (1, 4, 10, 17, 18, 29). Although increasing RV ejection pressure will increase RV ESV, this effect is only relevant when lung volumes increase enough to cause an increased pulmonary vascular resistance-induced increased Ppa (30). We did not see increases in Ppa. Hence, the slight increase in RV EDV measured after 5 s of increased Paw corresponds better to the assumed increase in Pms and the volume shifts taking place between the vascular compartments and ventricles.

The decrease in cardiac output generally found during PEEP ventilation may be explained by postulating that any increase in Pabd that is observed is insufficient to sustain an increased Pms because of inadequate intravascular volume. Clearly, the works of Cournand et al. (2) and others (4, 9, 26) have documented the need for adequate intravascular volume to maintain cardiac output when sustained increases in Paw are used. Also, Versprille and Jansen (33) showed the change in venous return to be volume dependent. A minor decrease in venous return was observed during inspiration in hypervolemic animals, whereas the ΔPra due to ventilation was the same during hyper- and normovolemic conditions.

Importantly, the thermodilution method as used with the pulmonary artery catheter measures RV output as pulmonary blood flow and not aortic blood flow as LV output. Clearly, the outputs of both ventricles may be markedly different from each other during times of varying venous return, although nearly identical when averaged over longer time intervals. Jansen et al. (14) demonstrated that patients being mechanically ventilated display a COava variation when thermal injections are timed at specific points in the ventilatory cycle that mirror instantaneous RV stroke volume measures (25). This transient RV flow pattern was recognized in some of our subjects when instrumented with a prototype pulmonary artery pulse contour catheter that estimated beat-to-beat changes in RV stroke volume. In fact, the changes in successive stroke volumes during the measurement period at the inspiratory-hold procedure were minimal and <5% (data not shown). Although not proving the accuracy of our system, these findings are consistent with them.

In summary, we found that, in hemodynamically stable fluid-resuscitated postoperative surgical patients, inspiratory-hold maneuvers with increases in Paw of up to 20 cmH2O have minimal effects on cardiac output, primarily because of an in-phase-associated pressurization of the abdominal compartment associated with compression of the liver and squeezing of the lungs.

REFERENCES


