Right atrial pressure as measure of ventricular constraint in newborn lambs

JEAN-CLAUDE FAUCHÈRE, ADRIAN M. WALKER, ELIZABETH M. SKUZA, AND DANIEL A. GRANT

Ritchie Centre for Baby Health Research, Monash Institute of Reproduction and Development, Monash University, Monash Medical Centre, Clayton, Melbourne, Victoria 3168, Australia

Received 28 February 2000; accepted in final form 24 January 2001

In the adult, ventricular constraint is amplified by decreasing chest wall and lung compliance, by increasing lung volume (17), and by the application of positive end-expiratory pressure (PEEP) (5, 14, 17). It is less certain how such changes in lung compliance, lung volume, and PEEP affect ventricular constraint in the newborn period. Nevertheless, clinical interventions, such as intermittent positive-pressure ventilation and PEEP, are widely used ventilatory strategies for babies with respiratory distress that may counteract the normal decrease in ventricular constraint that accompanies birth and thereby compromises cardiac function and vital organ perfusion.

Experimentally, ventricular constraint can be quantified by measuring pericardial pressure (P_{PER}) by using a liquid-containing balloon transducer positioned in between the pericardium and the heart (19). Clinically, it is seldom possible to directly measure pericardial pressure. However, a few intraoperative clinical studies (3, 24) support experimental studies (12, 20), which suggest that, at least in the adult, an estimate of P_{PER} can be obtained by measuring right atrial (RA) pressure (P_{RA}). We hypothesize that measurement of P_{RA} in the newborn is a useful estimate of ventricular constraint.

P_{RA} and thoracic inferior vena caval (IVC) pressure (P_{IVC}) are routinely measured in sick newborn infants and offer the potential to assess ventricular constraint. However, it is uncertain whether either of these pressures approximates pericardial pressure in the newborn. If P_{RA} or thoracic P_{IVC} reflect P_{PER} in the neonate, as they do in the adult, they may provide clinically useful tools for assessing ventricular constraint. Specifically, they would provide a means for assessing the effects that clinical interventions, such as volume therapy or mechanical ventilation, have on ventricular constraint. This may help predict their effect on cardiac function. In this study, we sought to determine whether either P_{RA} or thoracic P_{IVC} accurately reflects P_{PER} (and thus ventricular constraint) in the ventilated newborn (3-day-old) lamb. Because substantial cardiac remodeling occurs in the neonatal pe-
period, we also assessed whether $P_{RA}$ remains an accurate measure of ventricular constraint throughout the neonatal period by assessing this relationship in neonatal (4-wk-old) lambs. In addition, because ventilation is frequently manipulated in neonatal intensive care units, we sought to determine whether the relationship between $P_{RA}$ and $P_{PER}$ is maintained during alterations in PEEP.

**METHODS**

**Instrumentation**

All of the surgical and experimental procedures were performed in accordance with the guidelines established by the National Health and Medical Research Council of Australia (16), and were approved by the Monash Medical Centre Committee on Ethics in Animal Experimentation.

Twelve 4-wk-old Merino × Border-Leicester lambs (25–27 days, 11.6 ± 0.6 kg; means ± SE) and six 3-day-old lambs (2–4 days, 6.4 ± 0.4 kg) were anesthetized (5 mg/kg of ketamine and 100 mg/kg of α-chloralose for induction, followed by 25 mg·kg⁻¹·h⁻¹ of α-chloralose) and then intubated with auffed endotracheal tube. The lambs were placed supine and ventilated with a time-limited, pressure-controlled ventilator (model BP 200, Bourns; Riverside, CA). Ventilatory settings were adjusted to achieve normal blood gas and pH status. Body temperature (39.6°C ± 0.2) was monitored and maintained throughout the study with a warming blanket and a heating lamp.

The sternum was split and a 2-cm incision was made in the pericardium along the atroventricular sulcus. To record $P_{RA}$, we positioned a 3.5-Fr saline-filled umbilical venous catheter (Argyle, Sherwood Medical; St. Louis, MO) in the atrium through the right appendage and secured it with a purse-string suture. $P_{PER}$ was measured with the use of a calibrated (15), flat, liquid-containing Silastic balloon transducer (8, 19). This was positioned within the pericardial space overlying the free wall of the left ventricle (LV) in six of the 4-wk-old lambs and in all six of the 3-day-old lambs, and over the right ventricular (RV) free wall in the remaining six 4-wk-old lambs. The pericardial balloons were held in place with a single suture to the myocardium. The pericardial incision was loosely approximated with interrupted sutures. Care was taken not to artificially reduce pericardial volume.

No effort was made to seal the pericardium because the liquid-containing balloon transducers are known to accurately record pericardial pressure under these conditions in fetal, newborn, neonatal, and adult animals (7, 8, 10, 11, 19). The chest was then closed in layers, it was made airtight, and the trapped air was removed with 2–4 cmH₂O of continuous pressure. The transducer-tipped catheter and the strain-gauge manometer were connected to an amplifier and signal conditioner (Cyberamp 380, Axon Instruments; Foster City, CA). All of the physiological signals were low pass filtered at 100 Hz and continuously recorded on a thermal chart recorder (model 7758A, Hewlett-Packard; Waltham, MA). The signals were simultaneously digitized on a computer with a sampling rate of 200 Hz, with the use of an analog-to-digital converting board (model 4801/16, ADAC; Woburn, MA) and data acquisition software (CVSOFT, Odessa Computer Systems; Calgary, Canada).

**Protocol**

The experiments began after a 30-min recovery period and when normal arterial blood gas and pH status were attained. Each lamb was studied under two experimental conditions. First, we determined the relationship that existed between $P_{RA}$ and $P_{PER}$ over a range of LV end-diastolic pressures ($P_{LVED}$) when the lamb was exposed to a PEEP of 2.5 cmH₂O. $P_{LVED}$ was altered by rapidly withdrawing and subsequently reinfusing 180 ml of blood, followed by an additional infusion of 180 ml of donor blood or plasma substitute (Haemaccel, Hoechst Marion Roussel; Lane Cove, NSW, Australia). Second, we assessed whether the relationship between $P_{RA}$ and $P_{PER}$ remained constant when PEEP was increased. To do this, we repeated the procedures as described above, while maintaining PEEP at 15 cmH₂O. At the conclusion of the study, the lambs were euthanized with an overdose of pentobarbital sodium (150 mg/kg Lethabarb, Virbac Australia; Peakhurst NSW, Australia).

**Data Analysis**

One-second averages of all pressures were determined at end-expiration. Linear regression (least-squares method) was used to determine the slope of the relationships between $P_{RA}$ and $P_{PER}$, $P_{IVC}$ and $P_{PER}$, and between $P_{IVC}$ and $P_{RA}$. As shown in Fig. 1, $P_{LVED}$ equals the sum of the pressure across the ventricular wall, transmural $P_{LVED}$, and any forces applied to the ventricular wall by the surrounding tissues (recorded as $P_{PER}$). $P_{PER}$ equals the sum of the forces arising from the chest wall-lung combination (pleural pressure) and the forces arising from the pericardium (transpericardial pressure). Transmural $P_{LVED}$, an index of ventricular preload (11, 20, 21, 24), was calculated by subtracting $P_{PER}$ from $P_{LVED}$. Transmural $P_{LVED}$ was also calculated by subtracting $P_{RA}$ from $P_{LVED}$. It was then compared with the transmural $P_{LVED}$ that was calculated by using the balloon transducer.

The relationship between $P_{PER}$ and $P_{RA}$ and its possible dependence on age, location of measurement of $P_{PER}$ (LV vs. RV), and PEEP was investigated with the use of analysis of variance and analysis of covariance software (SPSS, version 6.1). This procedure involved comparing alternative regression models for fitting $P_{PER}$ data. All of the models incorporated $P_{RA}$ but the slopes and intercepts were allowed to vary according to age, location of measuring $P_{PER}$, animals, and PEEP.
P_LVED = P_LVEDtm + P_TP + P_PL

P_TV + P_PC = P_PER = Constraint

Fig. 1. At end diastole (ED), left ventricular (LV) pressure (P_LVED) equals the sum of the pressure across the ventricular wall, transmural P_LVEDtm and any forces applied to the ventricular wall by the surrounding tissues (recorded as pericardial pressure, P_PER). P_PER equals the sum of the forces arising from the chest wall-lung combination (pleural pressure, P_PC) and the forces arising from the pericardium (transpericardial pressure, P_TP). Increasing ventricular filling pressure might not be accompanied by increases in ventricular preload (transmural P_LVED) if P_PER increases at the same time.

RESULTS

Blood gas and pH values [pH 7.39 ± 0.01, arterial PO_2 131 ± 3 mmHg, arterial O_2 saturation (SaO_2) 98 ± 1%, arterial PCO_2 39 ± 1 mmHg, hemoglobin 8.2 ± 0.6 g/dl, base excess -1.4 ± 0.6 mmol/l] indicated a stable physiological preparation and appropriate ventilation. LV filling pressure varied from 0 ± 1 to 20 ± 1 mmHg by manipulating intravascular volume. In five of the lambs, P_LVED exceeded 20 mmHg, and in two of the lambs, P_LVED exceeded 25 mmHg. During each of these manipulations, P_PER, P_RA, and P_IVC closely tracked each other and, as such, a strong linear relationship existed between P_RA and P_PER, between P_IVC and P_PER, and between P_IVC and P_RA (Fig. 2).

The simplest regression model we considered was the one obtained by pooling the data from all lambs and plotting P_PER against P_RA. This explained 83.6% of the variation over the total of 3,320 (1 s) averaged data points. Accounting for age did not significantly improve the fit (F_{2,30} = 0.9, NS; not significant) explaining 84.4% of the total variation. Nor was the fit significantly improved by accounting for the location of the balloon transducer (LV or RV, 84.6% of the variation; F_{2,30} = 0.2, NS). Residual variation between animals accounted for 13.3% of the overall variation; thus the 18-regression line model (i.e., one line for each lamb) explained 97.9% of the total variation. Because each lamb was studied at two levels of PEEP, a 36-regression line model (i.e., separate regression lines for each animal and each level of PEEP) was also considered to assess the effect of increasing PEEP. The 36-regression line model accounted for an additional 1.32% of the total variation (P < 0.001). Finally, there was an average decrease in the slope of 0.06 and an average increase in the intercept of 1.0 between the 2.5 and 15 cmH_2O PEEP data. When incorporated into the 18-regression line model, this accounted for an additional 0.52% of the overall variation (P < 0.001), i.e., accounting for differences in slope and intercept associated with differences in PEEP accounted for ~40% of the improvement attained through the use of the 36-regression line model (39.4% = 100 × 0.52/1.32, F_{2,34} = 11.1; P < 0.001), nevertheless, PEEP only accounted for 1.3% of the total variation observed.

Because a linear relationship existed between P_RA and P_PER in all 12 of the 4-wk-old lambs we studied, regardless of whether the balloon transducer was positioned over the LV (Fig. 3A), or the RV (see Fig. 3B), and regardless of age, all of the data were combined to determine the average relationships (P_RA = 1.19 P_PER + 0.0, r = 0.99, P_IVC = 1.24 P_PER + 0.1, r = 0.99 and P_IVC = 1.0 P_RA - 0.2, r = 1.00).

The relationship between P_RA and P_PER largely remained constant regardless of the level of PEEP (P_RA = 1.19 P_PER + 0.0, r = 0.99 at 2.5 cmH_2O, and P_RA = 1.29 P_PER - 1.2, r = 0.98 at 15 cmH_2O). The same held true for the relationship between P_IVC and P_PER (P_IVC = 1.24 P_PER + 0.1, r = 0.99 at 2.5 cmH_2O, and P_IVC = 1.32 P_PER - 1.2, r = 0.97 at 15 cmH_2O), and between P_IVC and P_RA (P_IVC = 1.0 P_RA - 0.2, r = 1 at

Fig. 2. Linear relationships (r) existed between right atrial (RA) pressure (P_RA) and P_PER (left, P_RA = 1.22 P_PER - 0.6, r = 0.99), between inferior vena caval (IVC) pressure (P_IVC) and P_PER (middle, P_IVC = 1.21 P_PER - 1.1, r = 0.99) and between P_IVC and P_RA (right, P_IVC = 1.00 P_RA - 0.6, r = 1.0) for an experiment in a 4-wk-old lamb.
2.5 cmH2O, and \( P_{IVC} = 1.0 \ P_{RA} - 0.2, \ r = 1 \) at 15 cmH2O).

Elevations of \( P_{LVED} \) were accompanied by substantial increases in \( P_{PER} \) (\( P_{PER} = 0.71 \ P_{LVED} - 2.1, \ r = 1.0 \)) and in \( P_{RA} \) (\( P_{RA} = 0.66 \ P_{LVED} - 1.2, \ r = 1.0 \)). As a result, increases in transmural \( P_{LVED} \) were limited by the accompanying increases in ventricular constraint both when calculated as the difference between \( P_{LVED} \) and \( P_{PER} \) (transmural \( P_{LVED} = 0.29 \ P_{LVED} + 2.6, \ r = 1.0 \)) or \( P_{LVED} \) and \( P_{RA} \) (transmural \( P_{LVED} = 0.34 \ P_{LVED} + 1.6, \ r = 1 \); Fig. 4). No significant difference existed between the transmural \( P_{LVED} \) calculated with the use of these two measures of ventricular constraint (\( P_{PER} \) or \( P_{RA} \)) over the range of \( P_{LVED} \) common to all lambs (3–12 mmHg, Student’s paired t-test; \( P > 0.05 \)).

DISCUSSION

This study in ventilated newborn lambs demonstrates that \( P_{RA} \) and thoracic \( P_{IVC} \) accurately reflect \( P_{PER} \) and thus ventricular constraint over a large range of LV filling pressures. Moreover, our results show that the relationship between \( P_{RA} \) and \( P_{PER} \) is

---

Fig. 3. Relationship between \( P_{RA} \) and \( P_{PER} \) from each of the 4-wk-old lambs (\( n = 12 \)). There was a strong linear relationship between \( P_{RA} \) and \( P_{PER} \) in all lambs. Note that positioning the pericardial balloon transducer over the LV (A) or the right ventricle (RV) (B) did not significantly alter this relationship.

Fig. 4. Transmural \( P_{LVED} \) over the range of \( P_{LVED} \). Note that transmural \( P_{LVED} \) is limited by ventricular constraint in 4-wk-old lambs, as it is not incremented in a one-to-one fashion as \( P_{LVED} \) increases. Data are means ± SE from the 6 lambs, in which \( P_{PER} \) was recorded over the LV, calculated as transmural \( P_{LVED} = P_{LVED} - P_{PER} \) (●) and transmural \( P_{LVED} = P_{LVED} - P_{RA} \) (○).
maintained during development from newborn to neonate and during the application of PEEP. The strong linear relationship that we observed between $P_{RA}$ and $P_{PER}$ suggests that in the clinical setting of the neonatal intensive care unit, measurements of $P_{RA}$ can be used to monitor how clinical interventions affect ventricular constraint and therefore ventricular preload.

The relationship we observed between $P_{RA}$ and $P_{PER}$ is in keeping with earlier studies conducted in adult animals (12, 20) and adult patients (3, 24). Our validation of $P_{RA}$ as a measure of ventricular constraint in the newborn is of particular importance, given that in the adult, $P_{RA}$ can exceed $P_{PER}$ in the presence of ventricular hypertrophy (3, 24), and given that the fetal RV is relatively hypertrophied compared with that of the adult (18). This validation is also important given the substantial cardiac remodeling that occurs in the neonatal period. Our studies show that these changes do not influence the relationship between $P_{RA}$ and $P_{PER}$ in the newborn and neonatal period and that $P_{RA}$ can be used to assess ventricular constraint early in life. The range of $P_{RA}$ observed in our study span the range observed in adult human disease states. For example, our data exceed the range of $P_{RA}$ and $P_{PER}$ reported by Tyberg et al. (24) in adult patients undergoing coronary artery bypass and aortic valve replacement. Our data also span the range of pressures reported in patients with coronary artery disease, aortic stenosis, pulmonary hypertension, and cardiomegaly (3). Our observations indicated that the relation between $P_{RA}$ and $P_{PER}$ remained constant over a large range of $P_{LVED}$. Taken together, the results from adult studies and our current studies suggest that $P_{RA}$ may provide a useful measure of ventricular constraint in neonates and newborns with abnormal cardiovascular function. Additional studies will be needed to confirm this suggestion.

Acute changes in pulmonary artery pressure and pulmonary vascular resistance often occur in the sick newborn and it is important to consider how such changes may affect the $P_{RA}$-to-$P_{PER}$ relationship. On the basis of theoretical considerations, we predict that an acute increase in pulmonary artery pressure is unlikely to substantially alter the relationship between $P_{RA}$ and $P_{PER}$. When pulmonary artery pressure increases, and blood flow from the RV is impaired, $P_{RA}$ should also increase. As a result of an increase in RV volume and through the mechanism of ventricular interactions (22), $P_{PER}$ should increase an equal amount provided right atrial compliance remains relatively constant. Although experimental evidence suggests that this is the case, because acute changes in pulmonary artery pressure associated with pulmonary embolism in the adult do not alter the relationship between $P_{RA}$ and $P_{PER}$ (1, 2), future studies should assess this prediction in the newborn.

Umbilical catheterization of the sick premature neonate in intensive care is a routine clinical practice that would permit a simple assessment of ventricular constraint. Although positioning these catheters into the RA can be difficult, the relationship observed between $P_{PER}$ and $P_{IVC}$ reveals that both $P_{RA}$ and $P_{IVC}$ provide an accurate measure of ventricular constraint because an equally strong relationship existed between $P_{IVC}$ and $P_{PER}$ as that between $P_{RA}$ and $P_{PER}$. An ultrasound evaluation should be used to ensure that the catheter is truly placed within the RA or thoracic area with which the heart deforms the lungs or vice versa.

Although PEEP is known to alter ventricular constraint and limit cardiac function, in our study, as PEEP was increased, both $P_{RA}$ and $P_{PER}$ increased, and, as a result, the relationship we observed between $P_{RA}$ and $P_{PER}$ was largely maintained. Although accounting for the level of PEEP in our analysis significantly improved the fit of our regressions, the magnitude of this effect was small, accounting for 1.3% of the total variation. Thus the difference between the relationship of $P_{RA}$ and $P_{PER}$ at 2.5 and 15 cmH$_2$O PEEP was very small, i.e., in the 4-wk-old lambs, $P_{RA} = 1.14 P_{PER} + 0.0$ at 2.5 cmH$_2$O and $P_{RA} = 1.19 P_{PER} - 0.4$ at 1.5 cmH$_2$O and, as such, relating $P_{RA}$ to ventricular constraint remained valid during manipulations of airway pressure. This is of importance in the neonate, where ventilatory therapy can undergo many alterations to attain optimal gas exchange. Moreover, monitoring how $P_{RA}$ changes in response to ventilatory manipulations may prove useful in optimizing mechanical ventilation, while minimizing ventricular constraint.

Transmural $P_{LVED}$ was calculated on the basis of the balance of forces that exist in the LV at end diastole (Fig. 1) (8, 19, 21). Intravascular volume expansion increased both $P_{LVED}$ and $P_{PER}$. As a result, the increase in transmural $P_{LVED}$ that was observed was substantially limited by the increase in pericardial pressure (Fig. 4). The values of transmural $P_{LVED}$ are in keeping with previously reported levels of transmural $P_{LVED}$ in the newborn and neonatal lamb (7).

It has long been recognized that $P_{LVED}$ is not a reliable measure of ventricular preload (6, 11, 13, 20). In settings where ventricular constraint increases, such as during the application of PEEP (5, 14, 17), or when chest wall and lung compliance decrease (17), ventricular end-diastolic pressure overestimates ventricular preload. The alterations in the pressure-volume relationship of the heart that accompany the use
of PEEP may complicate the interpretation of ventricular function in the neonate (6). For example, if \( P_{LVED} \) were utilized to generate cardiac function curves before and after increasing PEEP and a downward shift in the cardiac function curve was observed, it would be interpreted as a decrease in contractility. However, if transmural \( P_{LVED} \) is used as the index of preload, the decrease in cardiac function is clearly explained by a decrease in preload acting via the Frank-Starling mechanism. Thus transmural \( P_{LVED} \) is a more reliable measure of preload than \( P_{LVED} \). In clinical settings, \( P_{RA} \) is often used as an index of ventricular preload. Just as \( P_{LVED} \) is limited as a measure of ventricular preload, so too is \( P_{RA} \). Elevated ventricular constraint may explain why cardiac function fails to improve in response to volume therapy in some sick neonates, although \( P_{RA} \) is increased. Appreciation of the magnitude of ventricular constraint in these situations would aid the clinician in selecting inotropic support rather than volume therapy. We have shown that in neonates transmural \( P_{LVED} \) can be accurately calculated as the difference between \( P_{LVED} \) and \( P_{RA} \). This validation provides the clinician with the means to directly assess ventricular preload in settings where \( P_{RA} \) and \( P_{LV} \) are recorded.

In conclusion, our study shows that measuring \( P_{RA} \) or thoracic \( P_{VC} \) provides a simple and accurate method of estimating pericardial pressure and assessing ventricular constraint in the newborn. Thus the information obtainable from variables routinely measured in the sick neonate has the potential to provide the clinician with a greater understanding of cardiac dysfunction in newborns undergoing intensive care. By measuring how \( P_{RA} \) changes with alterations in airway pressure, it may be possible to quantitate the effect of ventilatory therapies on cardiac constraint and help in optimizing ventilatory support, while minimizing cardiovascular dysfunction.

The authors thank Dr. P. J. Berger for editorial assistance.

J.-C. Fauchère was supported by the Overseas Postgraduate Research Scholarship (Department of Employment, Education, Training, and Youth Affairs, Australia), a Monash Graduate Scholarship (Monash University), a Herzog-Egli Stiftung Zurich; and by the Department of Education, Canton Zurich, Switzerland. D. A. Grant’s and A. M. Walker’s work was supported in part by the Monash Research Foundation for Mothers and Babies, in part by the National Health and Medical Research Council of Australia, and in part by the Monash Research Fund.

REFERENCES