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WITHIN-BREATH MODULATION OF LEFT VENTRICULAR FUNCTION DURING NORMAL BREATHING AND POSITIVE-PRESSURE VENTILATION IN MAN

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SUMMARY

1. To investigate how intrathoracic pressure affects left ventricular function during normal breathing and positive-pressure ventilation, beat-by-beat measurements of left ventricular stroke volume (LVSV; pulsed Doppler ultrasound), heart rate and blood pressure were made in five normal subjects breathing actively and then undergoing passive positive-pressure ventilation.

2. To assess the within-breath effects of positive-pressure ventilation on left ventricular function in the clinical setting, further measurements were made in six patients sedated, paralysed and ventilated because of brain injuries, who had no disease of the heart or lungs.

3. In the normal subjects, there was minimal phasic variation in LVSV during positive-pressure ventilation with the subject passive. Heart rate and blood pressure also stayed relatively constant throughout the ventilator cycle. During active breathing at the same depth and rate, there were large phasic respiratory variations in LVSV, with the lowest values occurring during inspiration.

4. In the paralysed and unconscious patients, an increase in LVSV was associated with the increase in airway pressure which occurred during lung inflation; however, the phase lag between the rise in airway pressure and the rise in LVSV varied widely between patients. These changes occurred whether or not sinus arrhythmia was present.

5. Addition of $4{\cdot}6 \pm 1$ cmH_2O of positive end-expiratory pressure (PEEP) did not increase the within-breath LVSV variations, but resulted in a mean depression of LVSV of 5·4% (paired t test, $P = 0{\cdot}035$).

6. The smaller variations in LVSV during positive-pressure ventilation compared to normal breathing in the conscious subjects may reflect (a) the smaller magnitude of positive, compared to negative, pleural pressure excursions which accompany a given tidal volume, and (b) an asymmetry between the effects of positive and negative pleural pressure on the heart.

7. The prominent effects of positive-pressure ventilation on LVSV in unconscious patients, compared to the minimal effects seen in ventilated normal subjects, may result from reduced lung compliance and a degree of pulmonary vascular congestion in the patients which was undetectable clinically or radiologically.

INTRODUCTION

Previous studies in man and animals have shown that raised intrathoracic pressure (IP) is associated with transiently enhanced left ventricular function, for example during the Valsalva manoeuvre (Fox, Crowley, Grace & Wood, 1966), positive-pressure inflation (Rankin, Olsen, Arentzen, Tyson, Maier, Smith, Hammon, Davis, McHale, Anderson & Sabiston, 1982; Okamoto, Komatsu, Kumar, Sanchala, Kubal, Bhalodia & Shibutani, 1986; Katzenburg, Olajos, Morkin & Goldman, 1986) or loaded expiration (Natarajan, Wise, Karam, Permutt & Wagner, 1987). Negative intrathoracic pressure, in contrast, reduces left ventricular ejection (Hoffman, Guz, Charlier & Wilken, 1965; Guz, Innes & Murphy, 1987). The detailed study of within-breath variations in left ventricular stroke volume (LVSV) is particularly difficult using techniques such as thermodilution (Okamoto *et al.* 1986) and radionuclide ventriculography (Natarajan *et al.* 1987) which are limited in temporal resolution and accuracy. Pulsed Doppler ultrasound, which enables continuous beat-by-beat measurements of LVSV to be made accurately and non-invasively (in selected subjects), has previously been used to study the effects of active breathing upon LVSV (Guz *et al.* 1987). In the current study this technique is used to describe the time course of LVSV changes during active breathing and positive-pressure ventilation in normal subjects, using the same breathing pattern and end-tidal P_{CO_2} (P_{ET,CO_2}). In addition, to assess the effects of positive-pressure ventilation on the heart in anaesthetized patients, LVSV changes were recorded in a group of patients with brain injuries on a hospital intensive care unit.

The results from the studies in patients have already been presented in preliminary form (Innes, De Cort, Kox & Guz, 1991).

METHODS

Normal subjects and patients

Five normal subjects (two females, three males; age range 26–40 years) took part in the first part of the study. In the second part of the study, data were obtained from six patients (four females, two males; age range 13–43 years) who were paralysed (Vecuronium, 3–6 mg h^{-1}), sedated (Midazolam, 1·5–4 $\mu g\ kg^{-1}\ min^{-1}$), intubated and ventilated following acute brain injuries (Table 1). Analgesia was given using Alfentanil, 0·5–1 $\mu g\ kg^{-1}\ min^{-1}$ according to the clinical need. These patients had no evidence of injury to the chest. Clinical examination of the heart and lungs was normal in all subjects and patients, and all the patients had normal chest X-rays. Ethical permission for the study was obtained from the Ethical Committee of Charing Cross Hospital.

Measurements

Left ventricular stroke volume was calculated from ascending aortic blood velocity (pulsed Doppler ultrasound; Pedof, Vingmed, Norway), multiplied by a measurement of aortic cross-sectional area (2-D echocardiograph; Irex, NJ, USA). This method has previously been validated for beat-to-beat measurements (Innes, Mills, Noble, Murphy, Pugh, Shore & Guz, 1987). Blood pressure was measured in the digital artery of the middle finger using a servo-controlled finger cuff (Finapres, Ohmeida, Englewood, CO, USA). Airway pressure (AP) was measured continuously either in the endotracheal tube (Validyne, CA, USA; in the patients) or, in the normal subjects, in the nasal mask used for ventilation (Gould, Statham). Changes in lung volume were measured using a DC-coupled respiratory inductance plethysmograph (Respitrace, Ambulatory Monitoring Inc, New York) in the patients, calibrated by reference to the ventilator settings, or with an ultrasonic airflow meter (Branta, Birmingham, UK) in the normal subjects.

In the patients, alveolar–arterial oxygen difference was calculated at the time of the measurements (using the alveolar gas equation) as a separate measure of the health of the lungs, and the central venous pressure was recorded as a measure of the state of circulatory volume expansion of the patients. In the normal subjects, to confirm relaxation during positive-pressure ventilation, diaphragmatic EMG activity was also monitored using surface electrodes (Neurolog; Lansing & Saville, 1989). Data were recorded on magnetic tape (Racal Store 7).

TABLE 1. Subject data

Subject No.	Sex	Age (yrs)	V_T (l)	AP (cmH_2O)	Compliance (l cmH_2O^{-1})	F_{I,O_2} (%)	P_{a,O_2} (mmHg)	A–a O_2 diff (mmHg)	Clinical diagnosis
					Normal subjects				
1	F	28	1·38	24·4	0·057				
2	M	26	1·42	20·9	0·068				
3	M	40	1·54	17·3	0·089				
4	F	28	1·54	16·7	0·092				
5	M	35	1·55	2·0*	0·119				
					Patients				
1	F	13	0·45	11·1	0·041	21	100	19	Head injury
2	F	24	0·44	17·4	0·025	21	101	16	Head injury
3	M	26	0·77	26·0	0·030	30	100	85	Head injury
4	M	43	0·63	14·0	0·045	30	79	86	Head injury
5	F	30	0·47	14·2	0·033	25	78	73	SAH
6	F	32	0·50	15·2	0·033	25	126	20	SAH

V_T, tidal volume; AP, airway pressure at end inflation; compliance, lung + chest wall compliance; F_{I,O_2}, fractional inspired oxygen (%); P_{a,O_2}, arterial oxygen partial pressure; A–a O_2 diff, calculated alveolar–arterial oxygen difference; SAH, subarachnoid haemorrhage.

* In this subject, oesophageal pressure was measured instead of airway pressure.

Experimental protocol

Normal subjects. The subjects lay in a semi-supine position (15 deg above horizontal), and were ventilated using a constant-volume ventilator (PneuPAC) by means of a nose mask at a rate of 13 breaths min^{-1} with an inspiratory to expiratory time ratio of approximately 2:3 and tidal volume ranging from 1·4 to 1·6 l. A higher tidal volume was necessary in the conscious subjects compared to the patients (see below) since the tidal volume used in the patients felt uncomfortably low. End tidal P_{CO_2} (P_{ET,CO_2}) was prevented from falling by use of a dead space of approximately 2 l, and varied between 34 and 42 mmHg. Before the study each subject was trained to be passively ventilated; passivity was judged (Datta, Shea, Horner & Guz, 1991) by a smooth and consistent airflow and airway pressure signal and absence of diaphragmatic EMG activity (Fig. 1). Several minutes of data were then recorded during (a) positive-pressure ventilation as described and (b) active breathing at the same rate and tidal volume with the same dead space. This matching was achieved using visual feedback of the integrated airflow signal recorded during positive-pressure ventilation, aided by the sound of the ventilator, which was left running although disconnected. In one subject, oesophageal pressure was also monitored (using an oesophageal balloon; Milic-Emili, Mead, Turner & Glauser, 1964) as a measure of pleural pressure. This subject was studied with the chest elevated at 60 deg to the horizontal to prevent the weight of the mediastinal organs from elevating the oesophageal pressure above the pleural pressure.

Paralysed and sedated patients. The patients lay supine and were ventilated (according to clinical needs) using a volume-cycled ventilator (Erica-Engström, Sweden) via an endotracheal tube. Respiratory rates varied from 10 to 16 breaths min^{-1} and tidal volume varied from 0·5 to 0·8 l, with an inspiratory/expiratory duration ratio of 1:2. Several minutes of data were recorded during the following conditions: (a) no positive end-expiratory pressure (PEEP); (b) PEEP applied at 5 cmH_2O (in one case 2·5 cmH_2O); (c) disconnection of the ventilator for one breath, then reconnection before the beginning of the next inflation. This was done six times in each of three patients.

Data analysis

For ventilated patients and normal subjects, data for an average of 56 ± 8 individual heart beats were analysed; the corresponding airway pressure and lung volume changes therefore extended over several respiratory cycles. To provide a detailed description of the dependence of LV function

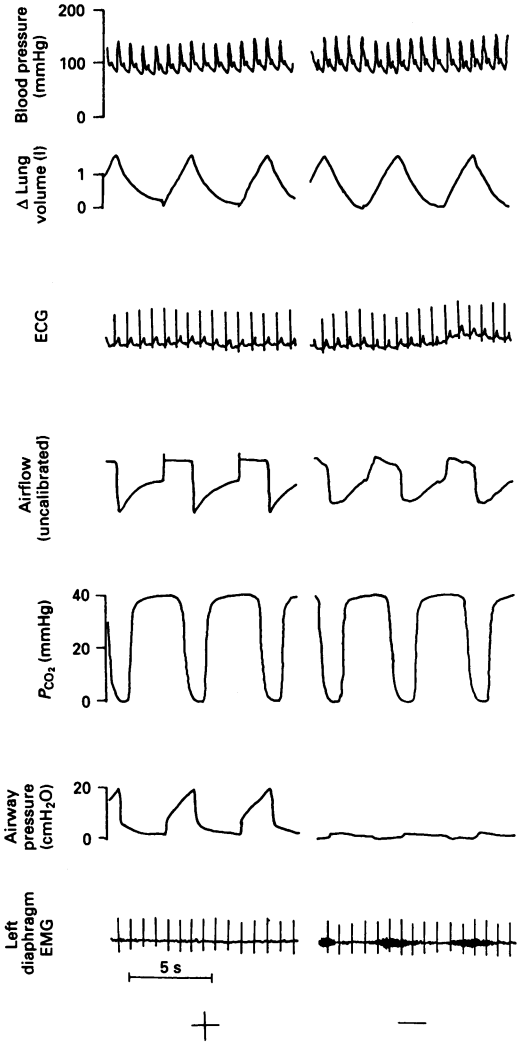

Fig. 1. Comparison of cardiovascular and ventilatory data obtained during positive-pressure ventilation (left, +) and active breathing (right, −) in normal subject No. 4. Lung volume, airflow and P_{ET,CO_2} are closely matched during active and positive-pressure ventilation. The EMG traces show an artifact due to the ECG. The ability of the subject to relax during positive-pressure ventilation is confirmed by (i) the absence of phasic respiratory activity in the diaphragmatic EMG and (ii) the smoothness and regularity of the airflow and mouth pressure signals.

on the respiratory cycle, each beat was plotted against the time between the start of inflation in the current breath and the peak of the ECG R-wave for that beat (QRS complex). To model the phasic respiratory component of the LVSV changes, the fundamental and first harmonic of a sine

wave (at the frequency of respiration) was fitted to the LVSV data (Fig. 2) for each patient by an iterative least-squares method (SPSS, Inc. Chicago, USA), using the equation:

$$\text{'Fitted' LVSV} = \text{mean LVSV} + A(\text{Sin}(X+B)) + C(\text{Sin}(2X+D)),$$

where A and C are the gain terms for the fundamental and first harmonic respectively, B and D are the corresponding lags (from the start of inflation), X is phase of respiration (in radians) relative to the start of inflation. The total variability with time of LVSV was measured as its coefficient of

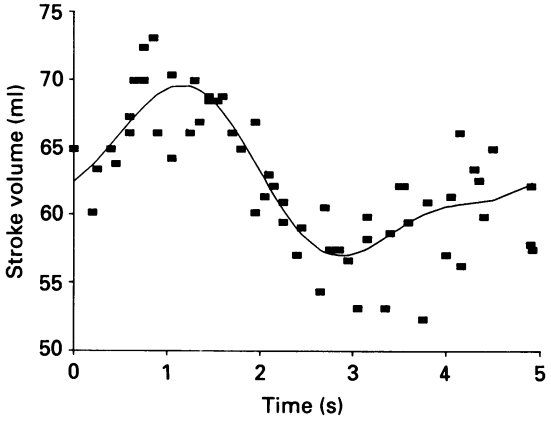

Fig. 2. Stroke volume data and fitted curve describing the phasic respiratory component of LVSV changes in one ventilated patient. Time 0 is the time of onset of lung inflation.

variation (c.v.; defined as the standard deviation as a percentage of the mean for that subject), and is composed of (i) random variations and (ii) phasic variations with the same period as respiration (secondary to intrathoracic pressure variations, sinus arrhythmia or other mechanisms; see below). The magnitude of the phasic component of the fluctuations was estimated as that proportion of the variability which was modelled by the fitted curves. This was derived by multiplying the c.v. (a measure of total variability) by R^2 from the curve fit (the fraction of the variability explained by the fitted curve). The phase relationship between ventilation and LVSV was also derived from the fitted curves. To illustrate the average result for each experimental condition, values of LVSV from the fitted curves were expressed as percentage differences from the mean LVSV in each subject and these percentages averaged across subjects for each phase of the respiratory cycle.

For experiments in which the ventilator was disconnected for one breath, data for five or six interventions were included in each subject. To combine the data from these interventions, data were time-aligned at the start of the missed inflation (this time was known since the duration of the ventilator cycle was constant) and values during the breath before the disconnection and two breaths after were plotted against time.

The static compliance of the respiratory system (lungs plus chest wall) was estimated from the increment in lung volume divided by the increment in airway pressure associated with a completed inflation (no airflow) in both the normal subjects and the patients.

RESULTS

Normal subjects

After appropriate training, all subjects were able to fully relax and tolerate positive-pressure ventilation while remaining passive. Passivity was continuously monitored by observing smooth and reproducible flow and pressure traces, and the absence of activity in the diaphragmatic surface EMG (Fig. 1).

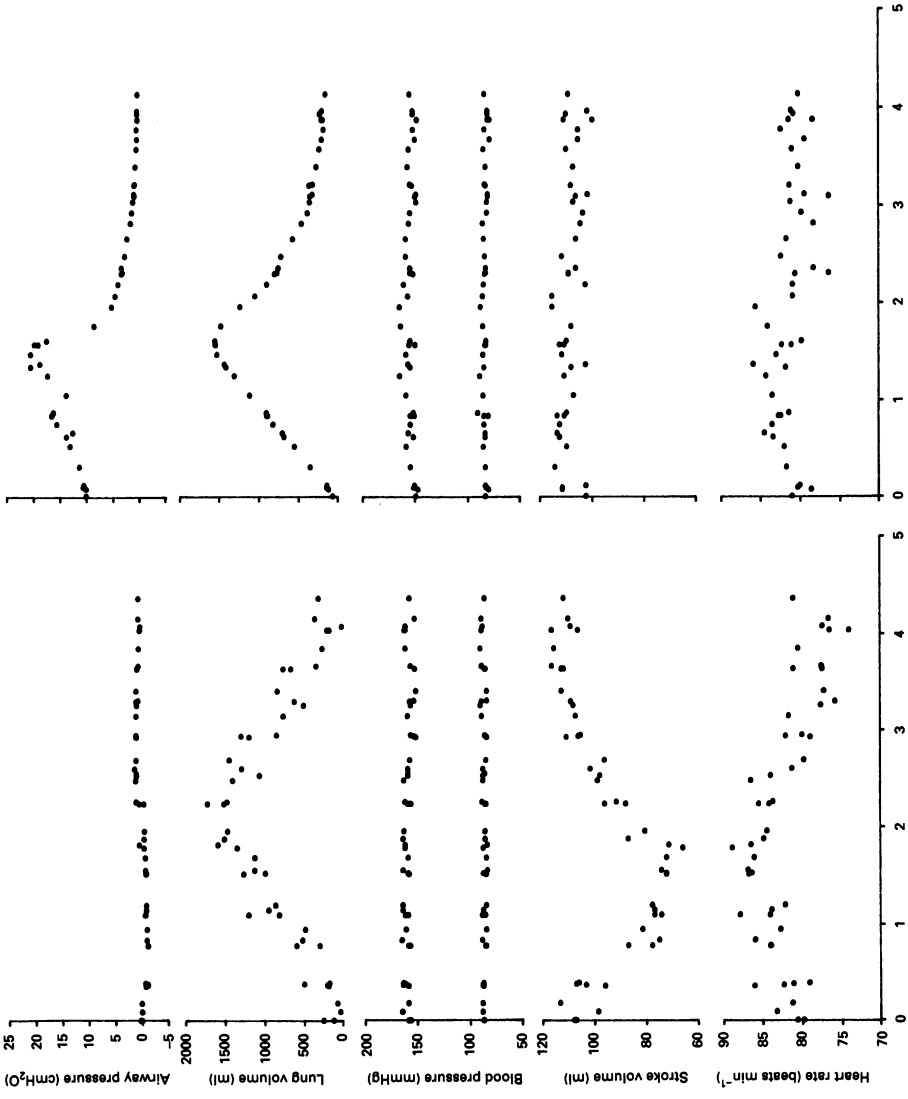

Fig. 3. Combined data for several respiratory cycles in a normal subject during active breathing (left) and positive-pressure ventilation (right). The prominent respiratory fluctuations in LVSV seen during active breathing are absent during positive-pressure ventilation with the same tidal volume.

Mean LVSV was lower during positive-pressure ventilation in each subject (72 ± 10 ml; mean $\pm$ S.D.) than during active breathing at the same rate and tidal volume (83 ± 20 ml). During active breathing, large respiratory variations in LVSV occurred; the total coefficient of variation of LVSV averaged 14·1%, while 11·0%

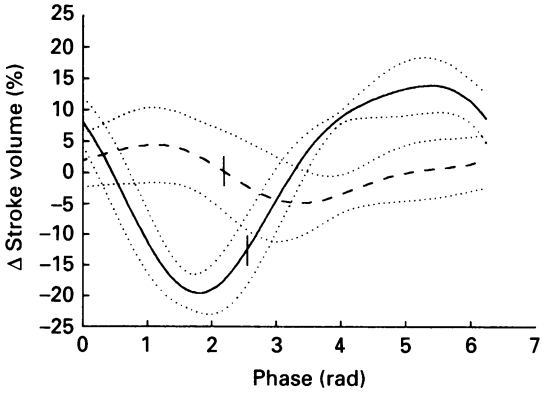

Fig. 4. Variations in LVSV during the respiratory cycle in a group of spontaneously breathing normal subjects (continuous line) and in a group of patients undergoing positive-pressure ventilation (dashed line). Each line is the mean of the fitted curves for all subjects in the group. The accompanying dotted lines show ± 1 S.D. of the mean response. The duration of the respiratory cycle is normalized to 2π rad, and 0 rad is defined as the onset of inspiration or lung inflation. Short vertical lines on each trace indicate the onset of expiration or lung deflation. During spontaneous breathing, low values of LVSV occur during inspiration. During positive-pressure ventilation in the patients, lung inflation is accompanied by increased values of LVSV.

was attributable to respiratory variation. LVSV was lowest during inspiration (Figs 3 and 4). During positive-pressure ventilation, however, there was little respiratory-related variation in LVSV in any subject (e.g. Fig. 3). The total c.v. averaged 5·1% for the group; only 1·1% could be explained by fitting curves at the frequency of respiration (see above). Within-breath variations in heart rate were also very much smaller during positive-pressure than during active ventilation (Fig. 3). Fluctuations in blood pressure were very small and inconsistent in phase during both positive-pressure and active ventilation. Static respiratory system compliance measured during positive-pressure ventilation varied from 0·057 to 0·119 l cmH_2O^{-1}, (Table 1); these values are normal (Comroe, Forster, Dubois, Briscoe & Carlsen, 1962).

Pleural pressure changes during positive-pressure ventilation

In one subject, oesophageal pressure was determined as an index of pleural pressure. During positive-pressure ventilation, oesophageal pressure (relative to atmospheric) rose from $-2{\cdot}5$ cmH_2O at end expiration to $+2$ cmH_2O at end inflation. During active breathing at the same rate and tidal volume, the oesophageal pressure swings were much larger, falling to -10 cmH_2O on inspiration, and rising to $+1$ cmH_2O during expiration.

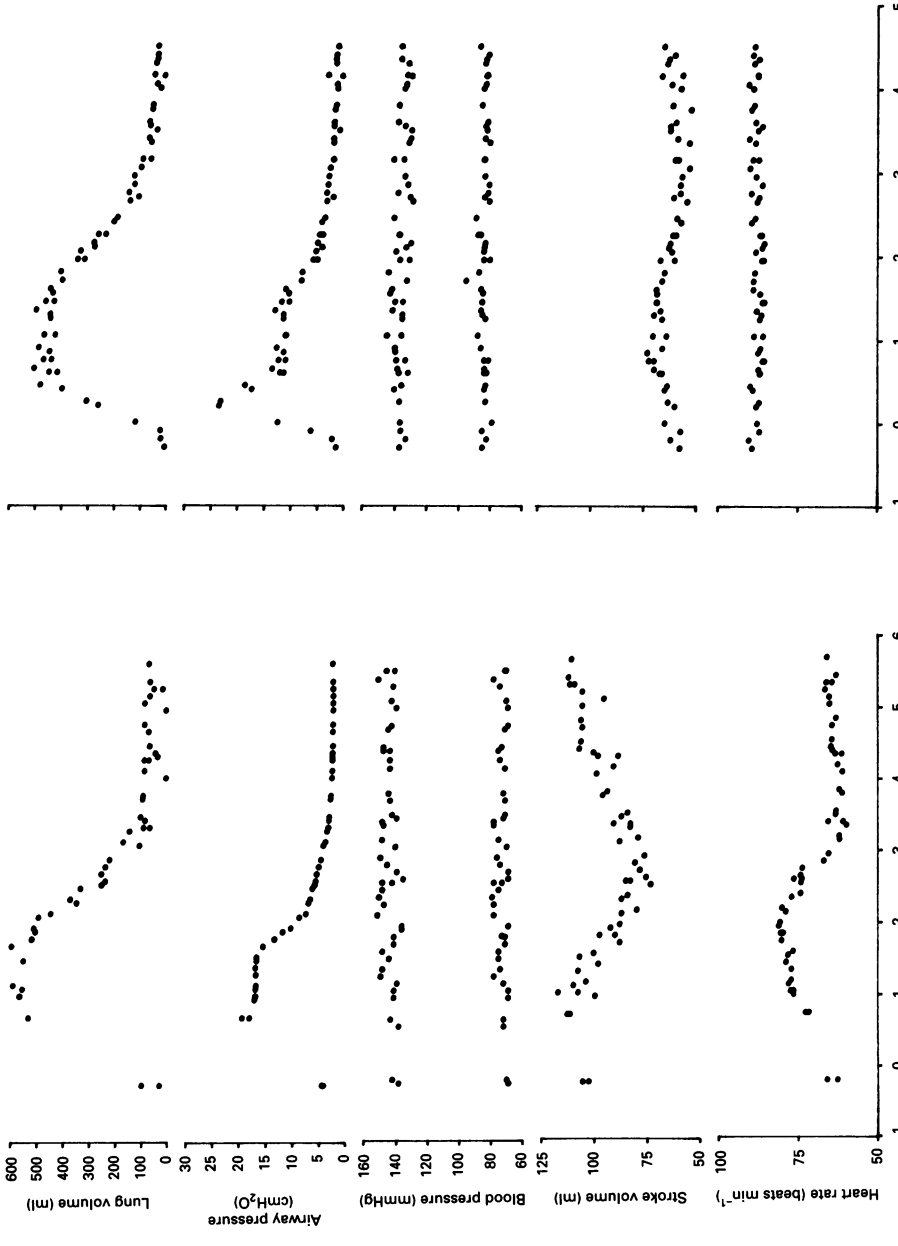

Fig. 5. Beat-to-beat cardiac data and simultaneously sampled respiratory data in two ventilated patients. Data for consecutive heartbeats over several ventilator cycles are plotted in relation to the time from the onset of inflation to the QRS complex of that heartbeat. The patient on the left shows prominent sinus arrhythmia; that on the right does not. Clear respiratory fluctuations in stroke volume are seen in both cases.

Paralysed and sedated patients

Condition of the respiratory system and circulation

As stated above, patients were selected who had normal hearts and lungs as judged by clinical examination and chest X-ray. Despite this, four of the patients were

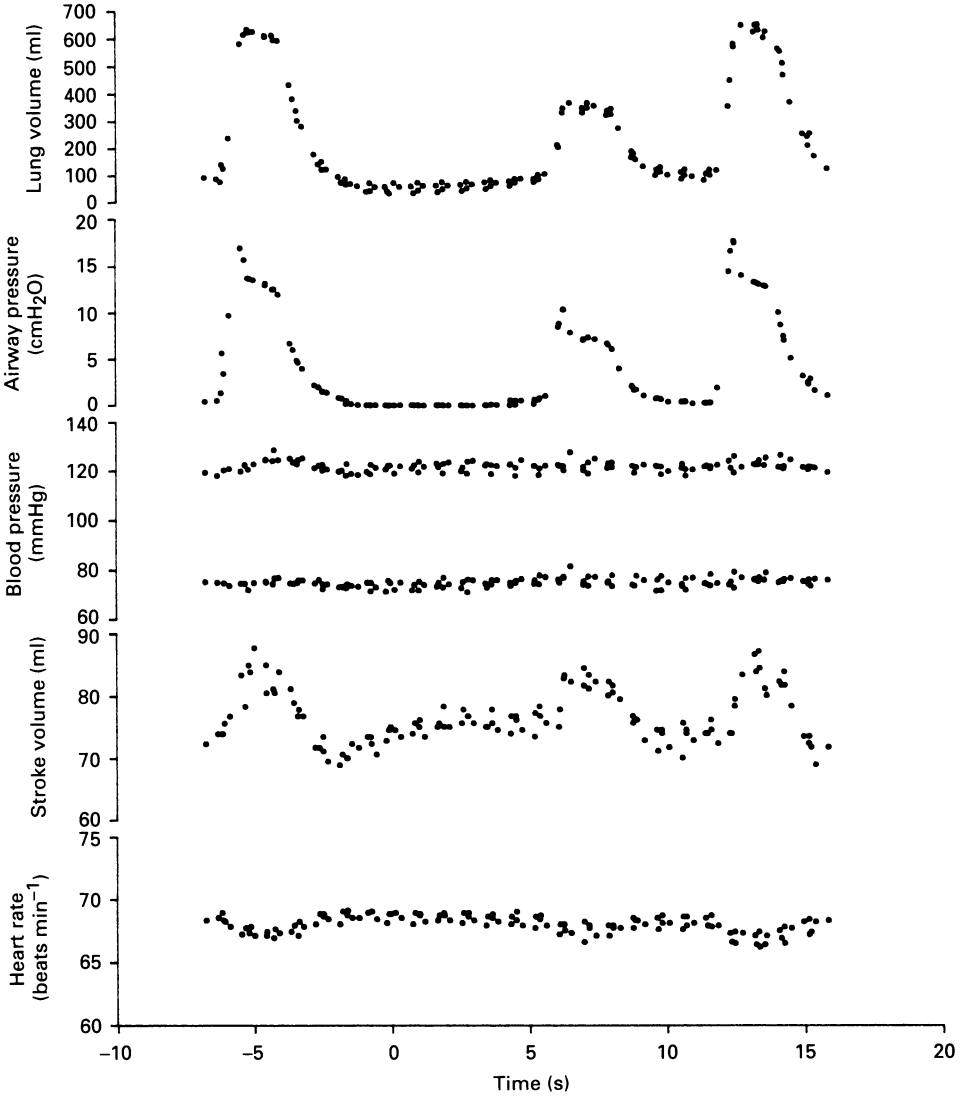

Fig. 6. Combined data for six runs in which the ventilator was disconnected for one breath, in one subject. Time 0 represents the time of the start of inflation of the missed breath. Following disconnection, the expiratory depression of LVSV recovers towards the mean value. Beats occurring immediately following the resumption of inflation show augmented LVSV.

receiving supplemental oxygen, and the alveolar–arterial oxygen difference at the time of study was significantly widened in three patients and slightly increased in the others (Table 1). In addition, the static compliance of the respiratory system was significantly lower than normal in the whole patient group (range 0·025–0·045 l cmH_2O^{-1}; Table 1). Central venous pressure (relative to the mid-axillary line) was $10·3 \pm 2·4$ cmH_2O (mean ± S.D.) in the group, indicating a 'full' central circulation.

Positive-pressure ventilation without PEEP

Left ventricular stroke volume varied with ventilation in each patient; two examples are shown in Fig. 5. Peak airway pressure during inflation reached between 18 and 30 cmH_2O. The sine wave curves fitted the LVSV data with R^2 values ranging from 0·39 to 0·83, and the magnitude of respiratory-related variability in LVSV was much greater in this group than in the normal subjects during positive-pressure ventilation, despite the normal subjects being ventilated at higher tidal volumes. The total coefficient of variation of LVSV in the patient group averaged 6·2%, with 4·1% explained by curves fitted at respiratory frequency. There were considerable differences between patients in the phase relationship between LVSV and lung volume, but on average, LVSV was increased during inflation and decreased during lung deflation (Fig. 4). This pattern of LVSV changes was the opposite to that seen during spontaneous breathing in the normal subjects, and occurred whether or not sinus arrhythmia was present (Fig. 5). There was little change in blood pressure during the ventilator cycle (Fig. 5).

Effect of positive end-expiratory pressure

During positive end-expiratory pressure ($4·6 \pm 1·0$ cmH_2O, $n = 6$), the mean LVSV fell by an average of 5·4% in the group ($P = 0·035$) and cardiac output fell by an average of 5·4% ($P = 0·034$, paired t tests). PEEP did not significantly change the magnitude of the within-breath variations in LVSV (during PEEP total c.v. was 6·5%, with 4·6% being attributable to phasic respiratory variation) or systolic blood pressure.

Effect of temporary disconnection

Following disconnection of the ventilator the depression of LVSV which accompanies lung deflation recovered towards the mean level. The results were very similar in all three subjects; an example is shown in Fig. 6. On reconnection of the ventilator, beats which occurred immediately following the onset of lung inflation showed increased LVSV.

DISCUSSION

This is the first reported study of beat-by-beat variations in LVSV during positive-pressure ventilation in man, although LVSV has previously been recorded in the same way during active breathing in conscious man (Guz *et al.* 1987).

During positive-pressure ventilation in unconscious patients, LVSV is greatest during inflation, whereas in conscious actively breathing subjects, maximal values of LVSV are associated with expiration. In conscious, passively ventilated normal subjects, however, there is little apparent respiratory variation in LVSV.

Previously proposed mechanisms for within-breath LVSV variations

Variations in the duration of LV filling due to variations in heart rate (i.e. sinus arrhythmia) could conceivably affect LVSV. The present data argue against this being an important mechanism since similar large variations in LVSV were seen in subjects with and without prominent sinus arrhythmia (Fig. 5); furthermore the phase and waveform of the variations in heart rate differed from the phase and waveform of the LVSV changes. The relative unimportance of sinus arrhythmia in the generation of LVSV variations was also shown by our previous observations in patients with dual-chamber pacemakers, who show marked LVSV changes with breathing when the heart rate is held constant (Guz *et al.* 1987).

Increases in lung volume achieved by normal breathing and by ventilation result in negative and positive IP excursions respectively, and are accompanied by changes in LVSV in opposite directions. This suggests that intrathoracic pressure determines the direction of LVSV changes irrespective of the direction of lung volume changes.

Effect of negative intrathoracic pressure on the left ventricle

The decrease in LVSV which occurs during spontaneous inspiration was originally thought to be due to pooling of blood in the lungs (as a consequence of increased pulmonary vascular capacitance; Hoffman *et al.* 1965; Wead & Norton, 1981) resulting in reduced LV filling, or preload. Direct measurements in animals demonstrate that pulmonary venous pressure falls during inspiration by approximately the same amount as intrathoracic pressure (Morgan, Dillard & Guntaroth, 1966). However, left atrial pressure falls rather less than intrathoracic pressure, i.e. a more positive transmural pressure develops in the left atrium (Summer, Permutt, Sagawa, Shoukas & Bromberger-Barnea, 1979). Left atrial transverse diameter increases slightly during inspiration (Katzenberg *et al.* 1986), but attempts to measure the effects of inspiration on pulmonary venous flow have produced inconsistent results (Morkin, Collins, Goldman & Fishman, 1965; Morgan *et al.* 1966) and this issue is not settled. The rise in left atrial transmural pressure suggests that inspiration impedes left ventricular filling, for which one suggested explanation is the concept of ventricular interdependence (Santamore, Lynch, Meier, Heckman & Bove, 1976; Robotham, Lixfield, Holland, MacGregor, Bryan & Rabson, 1978; Robotham & Mitzner, 1979). According to this theory, the gradient for systemic venous return increases during inspiration, leading to increased filling of the right ventricle. This effectively reduces LV compliance by causing displacement and stiffening of the interventricular septum; such displacement has been observed using echocardiography in man (Brinker, Weiss, Lappe, Rabson, Summer, Permutt & Weisfeldt, 1980). The physical constraint on heart size provided by the pericardium appears to contribute to interdependence of the ventricles since pericardectomy reduces interdependence (Robotham & Mitzner, 1979). Further support for the concept that left ventricular filling falls during inspiration comes from the radionuclide study of Kim, Ishida, Tsuneoka, Matsubara, Hiraoka, Takeda, Inoue, Kamada, Kimura & Kozuka (1987) which showed a decrease in left ventricular end-diastolic volume during spontaneous inspiration. In addition to mechanical effects on LV preload, inspiratory LVSV may be depressed by the reduction in IP relative to the pressure in the systemic circulation outside the thorax, causing increased

impedance to LV ejection (increased LV after-load), as demonstrated during loaded and non-loaded inspiration both in the dog (Robotham *et al.* 1978; Summer *et al.* 1979; Scharf, Brown, Saunders & Green, 1979; Robotham & Mitzner, 1979; Robotham, Rabson, Permutt & Bromburger-Barnea, 1979) and in man (Buda, Pinsky, Ingels, Daughters, Stinson & Alderman, 1979; Karam, Wise, Natarajan, Permutt & Wagner, 1984). The relative contribution of increased LV after-load and decreased LV filling may depend upon the degree of negative IP. During small decreases in IP, decreased filling predominates, whereas the influence of increased effective after-load on LVSV is mainly seen when large changes in IP are imposed (Scharf *et al.* 1979).

Effects of positive intrathoracic pressure on the left ventricle

Cournand, Motley, Werko & Dickinson showed as early as 1948 that positive pressure ventilation, especially with continuous positive airway pressure, depresses mean values of cardiac output over long periods in man. This agrees with the current results showing lower values of mean stroke volume and cardiac output during positive pressure ventilation with PEEP than without. The immediate effect of lung inflation, however, is said to be a transient increase in LVSV, mainly due to an increase in left ventricular filling (Natarajan *et al.* 1987). This increase in left ventricular filling may result from ventricular interdependence since it occurs at a time when right ventricular filling is reduced by the positive IP, because of the decreased pressure gradient for systemic venous return (Cournand *et al.* 1948; Jardin, Farcot, Gueret, Prost, Ozier & Bourdarias, 1983; Santamore, Heckman & Bove, 1984). Increased intrathoracic pressure should also augment left ventricular ejection by reducing the pressure gradient for ejection of blood from the left ventricle into the systemic circulation (reduced after-load: Robotham *et al.* 1978; Jardin *et al.* 1983); however, this has not been shown in other studies (Natarajan *et al.* 1987), and again, the relative contributions of increased pre-load and decreased after-load to enhanced LVSV may depend upon the magnitude of the increase in IP, resulting in the apparent conflicts in the literature.

Current work

Use of the pulsed Doppler ultrasound method has provided a detailed analysis of the temporal relationship between IP and LVSV. This relationship was qualitatively similar in all the positive-pressure ventilated patients, but there was wide variation between patients in the phase of the LVSV changes. Disconnection of the ventilator followed by reconnection after one ventilator cycle demonstrated that increased LVSV during lung inflation was an immediate consequence of positive-pressure inflation and not a delayed effect resulting from the previous breath or a preceding fluctuation in right ventricular output (Fig. 6). The wide variability in phase relationship between LVSV and ventilation probably results from the interaction of the multiple positive and negative influences on LV function (discussed above), each with its own time constant. Since we have no measurements of ventricular volume, this study does not help directly to distinguish diastolic from systolic mechanisms of within-breath LVSV variation.

Why were the variations in LVSV in the normal subjects so much smaller during positive-pressure ventilation than during normal breathing at the same tidal volume? The reason is probably that the heart is exposed to different magnitudes of pressure change in the two situations. In normal breathing subjects, it is impossible *a priori* to perform an experiment in which the same tidal volume is accompanied (a) by negative pleural pressure (active breathing) then (b) by the same magnitude of positive pleural pressure excursion (positive-pressure ventilation). This is because during active breathing, the negative pleural pressure is due to the compliance of the lungs and the resistance to airflow in the airways and apparatus, whereas during positive-pressure ventilation, the positive excursions in pleural pressure (for the same change in lung volume) are determined by the chest wall compliance. In the one subject in whom oesophageal pressure was measured, it fell by 11 cmH_2O during active breathing, but rose by only 4·5 cmH_2O during positive-pressure ventilation with a matched tidal volume of 1·55 l.

The conventional view is that it is pleural pressure (usually measured indirectly through the oesophageal pressure) which mediates the effects of breathing on the heart. The situation is further complicated by two studies in the dog where direct measurements of pericardial pressure were compared to simultaneous measurements of oesophageal pressure during positive-pressure ventilation (Prewitt & Wood, 1979; Marini, Culver & Butler, 1981). In both studies the pericardial pressure exceeded the oesophageal pressure during lung inflation by about 4 cmH_2O or 40%. Cassidy, Wead, Seibert & Ramanathan (1987) argue that changes in the geometry and compliance of the structures surrounding the heart (the 'cardiac fossa') during ventilation may cause the juxtacardiac pressure to differ significantly from the peripheral pleural pressure. There is also an apparent conflict between the large respiratory-related variations in LVSV seen during positive-pressure ventilation in the patients and the minimal respiratory LVSV variations seen during positive-pressure ventilation in the normal subjects. For ethical reasons, we were unable to measure pleural or oesophageal pressure in the patients. Furthermore in the supine posture of our patients, oesophageal pressure may be a poor measure of pleural pressure due to the mass of the mediastinal organs (Cherniak, Farhi, Armstrong & Proctor, 1955). We were, however, able to measure the compliance of the entire respiratory system, and values for the patients were on average half those found in the normal subjects, despite the fact that the patients had clinically normal lungs. Since patients were selected who had no evidence of chest wall injury and the respiratory muscles were relaxed by neuromuscular blockade, we may reasonably assume that their chest wall compliance was normal. Hence the observed reduced total respiratory compliance in these patients must represent abnormally low lung compliance. Such increased lung stiffness is well-recognized (Nunn, 1987) and may reflect altered pulmonary surfactant (Woo, Berlin & Hedley-Whyte, 1969) or dependent atelectasis which has been shown (using computed tomography) to occur early during ventilation in humans (Strandberg, Hedenstierna, Tokics, Lundquist & Brismar, 1986). This would result in an increased pressure gradient between the alveoli and the pleural space rather than increased pleural pressure relative to atmospheric pressure (as would occur with reduced chest wall compliance). Such atelectasis could also explain the widened values of alveolar–arterial oxygen

difference seen in three of the patients, by the mechanism of shunting (Hedenstierna, Lundquist, Lundh, Tokics, Strandberg, Brismar & Frostell, 1989).

Permutt and colleagues showed, using *in vitro* experiments on dog lungs, that the effects of lung inflation on pulmonary vascular volume and pressure depended critically on the state of vascular distension of the pulmonary circulation (Permutt, Howell, Proctor & Riley, 1961). They showed how in hypovolaemic lungs, the pulmonary blood volume rose with inflation, but with pulmonary vascular congestion, blood was expelled from the lungs by inflation; this would augment left ventricular filling. In the patients in the present study, the central venous pressure was kept at relatively high levels for therapeutic reasons, therefore, it is likely that the pulmonary circulation was well filled. The augmentation of LVSV seen in these patients during lung inflation may therefore have resulted in part from augmented filling of the LV by the above mechanism. Furthermore, an increased transpulmonary pressure gradient resulting from low pulmonary compliance may have exaggerated this effect.

In conclusion, the output of the human left ventricle is profoundly influenced by the prevailing intrathoracic pressure. Positive-pressure ventilation in patients produces marked swings in LVSV which would not have been predicted from experiments in passively ventilated normal subjects. This difference reflects the multitude of mechanisms linking LVSV to intrathoracic pressure. Firstly, airway pressure is variably linked to pleural pressure because of differences in lung compliance. In addition, the pleural pressure may differ significantly from the juxtacardiac pressure, which in turn can affect both left ventricular filling and ejection. Finally, distension of the lung tissue during inflation may alter pulmonary vascular capacitance and thereby alter left ventricular filling in a manner which depends on the prevailing pulmonary blood volume.

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