Respiratory modulation of cardiac time intervals

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SUMMARY To determine the effect of respiration on systolic and diastolic time intervals, simultaneous phonocardiograms, carotid pulse tracings, M mode echocardiograms, and respiratory curve tracings were measured in 25 healthy subjects. The positioning of each cardiac cycle in relation to the phase of respiration was assessed and the dependency of heart rate and cardiac time intervals on respiration was examined. Heart rate clearly varied over the respiratory cycle. Where necessary the time intervals were corrected for heart rate or RR interval. The systolic time intervals showed a stronger dependency on respiratory group than the diastolic time intervals. The decrease in left ventricular ejection time and increase in pre-ejection period and isovolumic contraction time during inspiration support the idea that a relative increase in afterload in inspiration determines left ventricular systolic function. Isovolumic relaxation time also showed cyclic behaviour whereas the left ventricular filling time was affected by inspiration only. Filling time increased significantly when there was a transition from expiration to inspiration during left ventricular ejection. It seems that when isovolumic contraction takes place in expiration the diastolic intervals of this cycle take on an expiratory character. The increase in filling can be viewed as a compensatory effect that partly offsets the loss of stroke volume during inspiration.

The stroke volume of the left ventricle decreases during normal inspiration. This decrease is reflected in changes in left ventricular systolic time intervals: studies with normal subjects and various groups of patients have shown an increase in the pre-ejection period and a simultaneous decrease in left ventricular ejection time during inspiration.1−3

The mechanisms proposed to explain the drop in systolic efficiency postulate a drop in left ventricular filling owing to a phase lag between increased right and left ventricular output,4 5 a decreased pulmonary venous return caused by pooling of the blood in the pulmonary vascular bed,6 or a leftward septal shift caused by increased right ventricular filling.7−8 More recently it has been suggested that the drop in pleural pressure during inspiration results in a relative increase in aortic9−11 or atmospheric12 pressure with respect to the left intraventricular pressure—this is equivalent to increasing the effective left ventricular afterload.

To obtain a clearer understanding of the mechanisms of the effects of respiration on the temporal events of the cardiac cycle we studied the changes of both the systolic and diastolic time intervals during the respiratory cycle in 25 healthy subjects. We aimed to study the temporal events more closely than before and, in the light of the increasing interest in diastolic function, to measure not only systolic but all cardiac time intervals.

Subjects and methods

We studied 20 men and five women (aged 20–36) with no clinical evidence or history of cardiac or pulmonary disease. We used a Hewlett Packard 77020A Ultrasound Imaging System with a paper speed of 100 mm/s to obtain the following strip chart recordings in each subject: electrocardiogram, phonocardiogram, carotid pulse tracing, M mode echocardiogram of the mitral valve, and respiratory curve (thermistor sensor) (fig 1). The subjects were given no instructions about breathing behaviour. While the subject was seated we recorded 50 consecutive heart beats. The following time intervals were mea-
suured to the nearest 5 ms: (a) RR interval; (b) left ventricular ejection time (LVET) from the onset of the rapid upstroke of the carotid pulse to the incisura; (c) isovolumic relaxation time (IVR) from the first high frequency vibration of the aortic component of the second heart sound (A2) to the onset of mitral valve opening; (d) left ventricular filling time (LVFT) from the onset of mitral valve opening to mitral valve leaflet coaptation; (e) total electromechanical systole (RA2) from the R wave of the electrocardiogram to A2; (f) the interval from mitral valve closure of the preceding beat to A2 (MVCA2).

Two time intervals were derived: (a) pre-ejection period (PEP) as RA2–LVET and (b) isovolumic contraction time (IVC) as MVCA2–LVET.

We used the respiratory curve to determine the start of inspiration and expiration. From this information we calculated the position of each heart beat in relation to the respiratory phase. The cardiac time intervals of each beat were assigned to one of eight groups according to the following criteria (fig 2):

**Group 1**—systole in the first half of inspiration.
**Group 2**—diastole in the second half of inspiration.
**Group 3**—transition from inspiration to expiration in diastole.
**Group 4**—transition from inspiration to expiration in systole.
**Group 5**—systole in the first half of expiration.
**Group 6**—diastole in the second half of expiration.
**Group 7**—transition from expiration to inspiration in diastole.
**Group 8**—transition from expiration to inspiration in systole.

Systole was defined as electromechanical systole (pre-ejection period and left ventricular ejection time) and diastole as the interval from aortic valve closure to mitral valve closure (isovolumic relaxation time).
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time and left ventricular filling time).

Each of the above groups defines a particular coupling of the respiratory and cardiac rhythms. The group notation 1 to 8 does not represent the natural time course of respiration.

STATISTICAL ANALYSIS

The dependency of heart rate and the various cardiac time intervals on heart rate and RR interval was determined by analysis of variance. Linear regression analysis was used to determine the dependency of the cardiac time intervals on heart rate and RR interval. Student's t test was used to determine the statistical significance of differences in intervals between consecutive cardiac cycles.

Results

The mean (SD) number of beats analysed per subject was 47 (4·8) and the mean number of respiratory cycles was 9 (2·7). Because of the variation in heart rate caused by respiration (p < 0·0001) we examined cardiac intervals for their dependency on heart rate and RR interval (table 1). Left ventricular ejection time and isovolumic relaxation time were more significantly associated with heart rate, and left ventricular filling time and isovolumic contraction time more with RR interval. In all further examinations of the results we corrected these variables for these associations.

Analysis of variance showed a significant difference between the groups for each interval (table 2). The difference was strongest for the systolic intervals (p < 0·0001), strong for filling time (p < 0·01), and slightly weaker for isovolumic relaxation (p < 0·05). Fig 3 shows the values of each cardiac time interval in each of the eight respiratory groups.

PRE-EJECTION PERIOD

Pre-ejection periods were longest at the transition from inspiration to expiration (group 4) and shortest at mid-expiration (group 8). The pre-ejection values within the second half of expiration (group 6–8) were approximately the same and increased progressively depending on the timing in inspiration.

ISOVOLUMIC CONTRACTION TIME

The results for the isovolumic contraction time generally resembled those for the pre-ejection period. Values reached a maximum slightly sooner, towards the end of inspiration (group 3), and remained at that level into expiration (group 4). Although at mid-expiration isovolumic contraction time fell to low values resembling those in the pre-ejection

Table 1 Linear regression of heart rate and RR interval against cardiac time intervals

<table>
<thead>
<tr>
<th>Interval</th>
<th>Heart rate</th>
<th>RR interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression</td>
<td>p</td>
</tr>
<tr>
<td>PEP</td>
<td>-0·43 x HR + 115·29</td>
<td>0·133 NS</td>
</tr>
<tr>
<td>IVC</td>
<td>-0·70 x HR + 112·74</td>
<td>0·005</td>
</tr>
<tr>
<td>LVET</td>
<td>-0·93 x HR + 311·99</td>
<td>0·0001*</td>
</tr>
<tr>
<td>IVR</td>
<td>-0·82 x HR + 145·54</td>
<td>0·0004*</td>
</tr>
<tr>
<td>LVFT</td>
<td>-6·50 x HR + 905·69</td>
<td>0·0000</td>
</tr>
</tbody>
</table>

(t = -13·86)

*Higher level of significance of the two regression equations (HR and RR) for each interval.

PEP, pre-ejection period; IVC, isovolumic contraction time; LVET, left ventricular ejection time; IVR, isovolumic relaxation time; LVFT, left ventricular filling time.

Table 2 Heart rate and cardiac time intervals: overall mean (SD) mean values, maximum and minimum values, and p values for respiratory groups 1–8

<table>
<thead>
<tr>
<th>Respiratory group</th>
<th>Mean (SD)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>p &lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>80·4 (9·75)</td>
<td>80·1</td>
<td>82·8*</td>
<td>82·0</td>
<td>82·2</td>
<td>80·8</td>
<td>79·3</td>
<td>78·9</td>
<td>77·2+</td>
<td>0·0001</td>
</tr>
<tr>
<td>RR</td>
<td>758 (90·5)</td>
<td>759</td>
<td>734†</td>
<td>742</td>
<td>742</td>
<td>754</td>
<td>768</td>
<td>770</td>
<td>793*</td>
<td>0·0001</td>
</tr>
<tr>
<td>PEP</td>
<td>81·2 (13·6)</td>
<td>80·3</td>
<td>83·1</td>
<td>84·1</td>
<td>85·0*</td>
<td>81·3</td>
<td>78·4†</td>
<td>79·0</td>
<td>78·5</td>
<td>0·0001</td>
</tr>
<tr>
<td>IVC</td>
<td>0·4 (11·4)</td>
<td>-0·4</td>
<td>2·9</td>
<td>4·6*</td>
<td>4·5</td>
<td>0·8</td>
<td>-2·3</td>
<td>-1·3</td>
<td>-5·3†</td>
<td>0·0001</td>
</tr>
<tr>
<td>LVETc</td>
<td>-0·3 (10·1)</td>
<td>-0·2</td>
<td>-1·7</td>
<td>-3·9</td>
<td>-4·0†</td>
<td>1·1</td>
<td>4·0*</td>
<td>2·4</td>
<td>0·8</td>
<td>0·0001</td>
</tr>
<tr>
<td>IVRc</td>
<td>0·4 (9·7)</td>
<td>2·4*</td>
<td>1·7</td>
<td>0·0</td>
<td>-1·0</td>
<td>-2·0†</td>
<td>0·5</td>
<td>0·2</td>
<td>1·0</td>
<td>0·05</td>
</tr>
<tr>
<td>LVFTc</td>
<td>-0·1 (19·5)</td>
<td>-0·2</td>
<td>-3·5†</td>
<td>0·2</td>
<td>-0·2</td>
<td>-0·6</td>
<td>-2·0</td>
<td>-0·2</td>
<td>5·9*</td>
<td>0·01</td>
</tr>
</tbody>
</table>

*Maximum. †Minimum.

HR, heart rate; c, corrected. See table 1 for abbreviations.
ISOVOLUMIC RELAXATION TIME

Isovolumic relaxation time did not vary as much as other intervals. It reached a maximum in the first half of inspiration (group 1) and a minimum in the first half of expiration (group 5).

LEFT VENTRICULAR FILLING TIME

The values for filling time showed little or no variation apart from the maximum value which occurred at the beginning of inspiration (group 8), and the minimum which occurred in the second half of inspiration (group 3).

Discussion

HEART RATE

In earlier studies of respiration and systolic time intervals, respiratory arrhythmia did not produce a significant change of heart rate between mid-inspiration, mid-expiration, and end-expirations. We believe that the difference between these results and the ones that we obtained may be because we compared the values of eight different respiratory phases rather than just the values during inspiration and expiration. We found that the greatest difference in heart rates occurred between beats at the changeover between expiration and inspiration (group 8, 77-2 beats/min) and those in the second half of inspiration (group 2, 82-8 beats/min) (table 2). We found no significant difference between mid-inspiratory (groups 1 and 2, 81-0 beats/min) and mid-expiratory (groups 5 and 6, 80-1 beats/min) heart rates (p < 0-1).

Posture may be another explanation for the differences between our study and earlier studies. Others have shown that several cardiac variables differ significantly depending on whether they are measured while the subject is supine or sitting. It is therefore not unreasonable to expect that respiration will have a greater effect on heart rate in the sitting position than in the supine. The difference between maximum and minimum heart rates was 5-6 beats/min; this was considerably higher than the difference measured by others in supine subjects.313

SYSTOLIC TIME INTERVALS

Our results confirm previous studies that found a decrease in left ventricular ejection time and a simultaneous increase in the pre-ejection period during inspiration. An understanding of the effect of inspiration on systolic function aids the interpretation of these results. An increase of relative afterload owing to the decrease in pleural pressure would require a longer period of contraction to overcome this relative increase in aortic pressure. This delay in aortic valve opening is reflected in the
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increase of both the pre-ejection period and the isovolumic contraction time. For the same reason the aortic valve will close sooner, resulting in shorter ejection times. On the other hand, when pleural pressure conditions are reversed at the beginning of expiration, the values of the systolic time interval are reversed.

The behaviour of these intervals is symmetrical except for the second half of expiration. It is not obvious why ejection values become progressively smaller. Furthermore, in the second half of expiration pre-ejection period values remain relatively constant and isovolumic contraction produces a markedly lower value at the changeover between expiration and inspiration. As mid-expiration seems to be the turning point for these developments, we studied the beats in the second half of expiration more closely. We examined two consecutive beats when inspiration began during the isovolumic relaxation or filling time (that is in diastole) of the second beat. The systoles of both beats therefore lay in the second half of expiration. Table 3 shows that the systolic time intervals of these two beats were not significantly different. We assume, therefore, that the variation in the values of systolic time interval in the second half of expiration (groups 6 and 7) is more or less random. This could well be a result of the intrathoracic pressure conditions produced by end expiratory apnoea.

We also studied the pronounced drop in the isovolumic contraction time in group 8 by examining consecutive beats in which the inspiration started in systole (that is during either isovolumic contraction or ejection time). When inspiration started in the ejection time of the second beat, the duration of this interval decreased significantly (p < 0·01). Isovolumic contraction also shortened, although not significantly. The drop in both values (when a drop in one value would be expected to be accompanied by an increase in the other) can be explained by the fact that isovolumic contraction still occurs in expiration whereas ejection time is already affected by the inspiratory drop in pleural pressure. This means that the opening of the aortic valve occurs under expiratory pleural pressure conditions whereas there is premature closure of the aortic valve because of the increasing left ventricular aortic pressure gradient. This would explain why the value for isovolumic contraction time in group 8 is low; that it is the lowest may merely be the result of the end-expiratory fluctuation found in groups 6 and 7 (see above).

If all of systole occurs in inspiration—that is inspiration starts during isovolumic contraction and both intervals are affected by the decrease in pleural pressure—the difference in isovolumic contraction time between the two beats increases, whereas the difference in ejection time decreases. These differences were not statistically significant; but this was probably because there were too few subjects in whom inspiration started during isovolumic contraction for such a difference to become apparent (table 3).

DIASTOLIC TIME INTERVALS

The high levels of significance for the associations between systolic time intervals and phase of respiration reflect the fact that the contractile phase of the cardiac cycle is more dependent on respiration than the relaxation and filling phase. Analysis of variance showed that the isovolumic relaxation time, although dependent on respiration, is the least affected of all the cardiac time intervals. In normal subjects this interval was reported to be stable during and after exercise; this was also true over a large range of RR intervals in patients with atrial fibrillation. 20 21 The isovolumic relaxation time, however, varies increasingly in patients with ischaemic heart disease, left ventricular hypertrophy, hypertrophic cardiomyopathy, or aortic valve disease. 19 This shows that heart disease may affect respiratory modulation of isovolumic relaxation.

The peak isovolumic relaxation values did not occur in the respiratory groups in which the peak values of the other intervals were found. The maximum and minimum values occurred when other intervals were changing. The mechanisms of this phase shift are not clear.

Left ventricular filling time is strongly dependent on RR interval (that is heart rate). 19 20 After correction for RR interval the filling times reflect this strong dependency over most of the respiratory cycle. The higher values at the start of inspiration and the lower values in the second half of inspiration
imply that respiration induces changes in filling of the left ventricle. Previous studies in which the end diastolic volume, area, or dimensions were measured by sonomicrometer measurements, mechanical transducers, or echocardiography during normal inspiration found either no change or a decrease in these diastolic variables. A shortened filling time in the second half of inspiration does not contradict these findings. However, the increase in filling at the start of inspiration is unexpected. But the earlier studies did not consider beats in which inspiration started. It was in these beats that filling time was significantly prolonged (table 3). In such beats the ejection time is immediately shortened by the increasing pressure gradient between left ventricular and aortic pressure. The next isovolumic relaxation remains effectively unchanged and the filling time is significantly prolonged. This may be explained by the efficient initial contraction of the left ventricle during the isovolumic contraction which still takes place in expiration—that is before the relative increase in afterload occurs. The lack of change in isovolumic relaxation is consistent with the model of a coupling between contraction and relaxation. This coupling has been described on the basis of the release and subsequent uptake of calcium by the sarcoplasmic reticulum. More recently it has also been postulated that during contraction energy stored in the microstructure of the cardiac muscle cell and in the connective tissue surrounding the cells is released during diastole actively to relax and expand the heart. This energy stored during the end expiratory isovolumic contraction would accordingly result in an unchanged isovolumic relaxation despite the fact that inspiration has already begun. It would also maintain the factors responsible for fast filling during end expiration and, together with the fact that the left atrium is still well filled, lead to a filling time typical of end expiration. Apart from a shortened ejection time, such beats would therefore display the characteristics of an end expiratory beat. The decrease in ejection time implies a shorter RR interval and, as filling time is highly dependent on RR interval, the corrected filling time is in fact longer than it would normally be for a beat of this duration. If on the other hand a beat occurs completely after the start of inspiration, the intrathoracic pressure affects not just ejection but the complete left ventricular systole, with the consequences for relaxation and filling (table 3).

The measurement of the cardiac time intervals over the complete respiratory cycle leads to a better understanding of the respiratory modulation of the systolic time intervals. The results accord with the idea that a relative increase in afterload is the primary factor influencing left ventricular systolic function during inspiration. We also found changes in the diastolic time intervals that had not previously been reported, particularly in filling behaviour at the start of inspiration. This may be viewed as having a compensatory effect. At the transition from expiration to inspiration the RR interval shortens considerably. Because the filling time is highly dependent on RR interval, filling time would normally decrease more than the other intervals. When inspiration occurs in ejection time, however, only this interval shortens whereas the other intervals maintain their expiratory character. Therefore filling time is de facto longer than it would normally be for a beat of this length. An increase in filling at this point in the respiratory cycle would help to offset in part the loss of efficiency of left ventricular function during inspiration.

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