Determinants of heart rate variability in heart transplanted subjects during physical exercise

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Respiratory sinus arrhythmia has been described in heart transplanted subjects. In order to investigate the mechanisms involved in the generation of this condition in the transplanted heart and its evolution after surgery, graded exercise was performed (0-75 W in 25 W steps) on a cycle ergometer by 41 subjects (mean age 44 years) who had undergone heart transplantation 28 months (range 3-60) earlier and by six age matched-control subjects. R-R interval, respiratory signal, O₂ consumption (VO₂) and CO₂ production (VCO₂) were measured. Respiratory sinus arrhythmia was assessed by the autoregressive power spectrum of the R-R interval and respiration. All subjects reached the anaerobic threshold (heart transplants: 60% at 50 W, 40% at 75 W Controls: 150 W). In control subjects, the respiratory sinus arrhythmia was higher than in heart transplanted subjects (5-80 ± 0-30 vs 1-45 ± 0-16 In ms²), and it decreased significantly (4-66 ± 0-30 In ms², P<0.05) during exercise, despite the increase in breathing rate and depth. When the group of heart transplanted subjects was considered as a whole, respiratory sinus arrhythmia was found to be present in all conditions. It significantly increased at 25 W (from 1-45 ± 0-16 to 2-00 ± 0-17 In ms², P<0.01), then significantly fell below baseline during recovery (to 0-97 ± 0-23 In ms², P<0.01). Multiple regression analysis showed that a linear combination of heart rate (inverse correlation) and VO₂ (direct correlation) together with months having passed since transplantation surgery, could explain the observed changes in heart rate during exercise (multiple regression: r=0-658, P<0.0001). In five long-term transplanted subjects, non respiratory-related low frequency (0-1 Hz) waves were present on the R-R spectrum, but respiratory sinus arrhythmia is also present in the recently transplanted heart and depends on the opposing effects of ventilation and heart rate. In a few cases, sympathetic modulation (re-innervation) could not be excluded.

Key Words: Autonomic nervous system, respiratory sinus arrhythmia, power spectrum analysis, heart transplantation, heart rate variability.

Introduction

Consistent rhythmic changes in the R-R interval have been found recently in a number of heart transplanted subjects[1], and it has been suggested that a mechanism intrinsic to the heart, based on atrial distension, linked to respiratory-related venous return changes, could modulate heart rate in the denervated heart. The aim of this study was to compare, in control subjects and in a large population of heart transplanted subjects, changes in R-R interval non-causal oscillations during physical exercise, and to study R-R interval non-causal oscillatory components after a period of time had elapsed since the transplantation. Power spectrum analysis[2-4] of the R-R interval and respiration was used to identify and quantify the different components of heart rate variability (i.e. respiratory and non-respiratory sinus arrhythmia).

Methods

Subjects

Forty-one orthotopic heart transplant recipients and six age-matched control subjects were studied. Their characteristics are illustrated in Table 1. All the heart transplant recipients were treated with cyclosporine and oral steroids; eight of them were taking ACE inhibitors and six of them calcium antagonists for hypertension. The transplant recipients had neither signs or symptoms of active cardiorespiratory disease, other than controlled...
Table 1 Characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>6</td>
<td>41</td>
</tr>
<tr>
<td>Months ± SD (range)</td>
<td>28 ± 23(60)</td>
<td>28 ± 2(3-60)</td>
</tr>
<tr>
<td>Recipient age (years) ± SD</td>
<td>49 ± 2</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>Donor age (years) ± SD</td>
<td>24 ± 2</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>SBP (mmHg) ± SD</td>
<td>119 ± 6</td>
<td>138 ± 3</td>
</tr>
<tr>
<td>DBP (mmHg) ± SD</td>
<td>78 ± 4</td>
<td>93 ± 3</td>
</tr>
</tbody>
</table>

SBP=systolic blood pressure; DBP=diastolic blood pressure.

systemic hypertension (14 cases). Endomyocardial biopsy showed no evidence of tissue rejection at the time of the study. The protocol was approved by the local Institutional Review Board for Human Experimentation, and all subjects gave informed consent.

Protocol

The subjects remained in the sitting position on a cycle ergometer during the entire protocol. After 15 min of rest, exercise was performed in 25 W increments to exhaustion. Each step lasted 5 min, in order to allow the subjects to reach and maintain steady state working conditions for at least 2 min. The steady state condition was assessed by continuous monitoring of mean heart rate. When exercise ceased, recovery was monitored for 10 min. Conventional 12 lead electrocardiographic (ECG) recordings were obtained while the subjects breathed into a mouthpiece connected to a Medgraphics CPX (St. Paul, MN, U.S.A.) respiratory analyser. The device calculated breath-by-breath oxygen consumption (VO₂), CO₂ production (VCO₂), and respiratory rate, and continuous monitoring of the respiratory signal was obtained by an impedance pneumograph. Systolic blood pressure measurements were obtained at each step of the protocol using a conventional sphygmomanometer. ECG lead II and respiratory signals were recorded on FM tape throughout the procedure (3964A four channel FM recorder, Hewlett-Packard, Palo Alto, CA, U.S.A.).

Data collection and analysis

The data were digitized off line by a 12 bit analogue-to-digital converter (NB-MIO-16 board, National Instruments, Austin, TX, U.S.A.) at a sampling rate of 500 samples s⁻¹. The converter was connected to a Macintosh II computer (Apple Inc, Cupertino, CA, U.S.A.) equipped with 5 Mb RAM memory and a 60 Mb hard disk. A 'C' language program identified all the QRS complexes in each sequence and then located the peak of each R wave. The R-R intervals were obtained from these data, and for each step of the protocol 256 R-R intervals were analysed. During exercise at 25 W we evaluated the first and last 256 R-R intervals and thereafter only the last 256 R-R intervals for each step in order to obtain the most stable data. During recovery, data were obtained after 5 min had passed. The non-oscillatory (dc) component and slow trends were removed from each sequence as previously described⁵,⁶. The respiratory signal obtained by the impedance pneumograph was expressed in arbitrary values (mV output from the device). Only the signal that occurred at the peak of the R wave was measured. With this procedure, the respiratory signal can be constructed from a small number of samples, corresponding one-to-one to the R-R interval, as previously reported⁷-⁹. Premature beats were interactively identified and corrected by linear interpolation with the previous and following beats. The R-R interval data were then stored for further analysis.

Power spectral analysis and heart rate variability

We applied power spectral analysis to both R-R interval and respiratory signals, using an autoregressive model, as previously described¹⁰, and model coefficients were evaluated according to the Burg algorithm¹¹. Model order was assessed by Akaike criteria as previously suggested³,¹¹, and in most cases, a model order of 11 was found to be adequate. Spectral components were obtained by a decomposition method, previously described¹²,¹³, to measure the area below each spectral peak¹³. The frequency was expressed in Hz by assuming the mean R-R interval was a sampling interval. The respiration-related oscillations on the R-R interval spectrum in the range between 0·18–0·40 Hz (index of respiratory system arrhythmia) were identified by their correspondence with the oscillations on the respiratory spectrum. In most heart transplant subjects, only respiration-related oscillations were present, i.e. the previously defined²-⁴ high frequency component of the R-R interval and respiratory spectrum. They were therefore evaluated only in original units (ms²) rather than in normalized units, as in normal subjects¹⁰. In addition to the R-R power spectrum we evaluated heart rate variability as the standard deviation of the R-R interval.

Coherence analysis

The squared coherence function is a mathematical cross-spectral method for evaluating the stability of the phase relationship between the R-R interval and respiration. It was evaluated by an autoregressive algorithm, using the method described in detail by Baselli et al¹⁴. This function spans from 0 (no relationship from the two signals) to 1 (strong relationship) and we assume that only spectral components with high squared coherence (>0·5) demonstrate a significantly stable phase relationship between the instantaneous R-R interval and respiration, and hence a link between R-R interval.
Table 2 Exercise results: control subjects

<table>
<thead>
<tr>
<th>Heart rate (beats. min⁻¹)</th>
<th>R-R mean (ms)</th>
<th>R-R SD (ms)</th>
<th>HF (ln ms²)</th>
<th>LF (ln ms²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 70 ± 4</td>
<td>865 ± 54</td>
<td>48 ± 5</td>
<td>5·80 ± 0·30</td>
<td>6·90 ± 0·2</td>
</tr>
<tr>
<td>50 82 ± 4*</td>
<td>736 ± 38*</td>
<td>34 ± 3</td>
<td>4·66 ± 0·30</td>
<td>6·10 ± 0·52</td>
</tr>
<tr>
<td>75 93 ± 6**</td>
<td>657 ± 40**</td>
<td>23 ± 7**</td>
<td>3·89 ± 0·46</td>
<td>5·81 ± 0·27*</td>
</tr>
<tr>
<td>100 106 ± 7***</td>
<td>577 ± 35***</td>
<td>17 ± 2***</td>
<td>3·42 ± 0·40</td>
<td>5·10 ± 0·31***</td>
</tr>
<tr>
<td>125 120 ± 9****</td>
<td>511 ± 35***</td>
<td>11 ± 1***</td>
<td>2·67 ± 0·57</td>
<td>4·28 ± 0·27***</td>
</tr>
<tr>
<td>150 136 ± 9*****</td>
<td>450 ± 29*****</td>
<td>8 ± 1***</td>
<td>2·01 ± 0·58</td>
<td>3·33 ± 0·53***</td>
</tr>
<tr>
<td>Recovery 114 ± 8**</td>
<td>541 ± 43**</td>
<td>19 ± 2**</td>
<td>2·81 ± 0·45</td>
<td>4·54 ± 0·52**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LF/HF</th>
<th>SBP (mmHg)</th>
<th>VO₂ (ml. kg⁻¹min⁻¹)</th>
<th>AT (VO₂/VO₂CO₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3·95 ± 1·16</td>
<td>119 ± 6</td>
<td>3·64 ± 0·12</td>
</tr>
<tr>
<td>50</td>
<td>5·04 ± 1·24</td>
<td>132 ± 7****</td>
<td>8·15 ± 0·35***</td>
</tr>
<tr>
<td>75</td>
<td>5·71 ± 2·20</td>
<td>141 ± 8****</td>
<td>11·68 ± 0·57***</td>
</tr>
<tr>
<td>100</td>
<td>7·33 ± 3·91</td>
<td>148 ± 8****</td>
<td>15·10 ± 0·54***</td>
</tr>
<tr>
<td>125</td>
<td>7·31 ± 3·65</td>
<td>164 ± 9****</td>
<td>19·29 ± 0·23***</td>
</tr>
<tr>
<td>150</td>
<td>4·35 ± 2·59</td>
<td>183 ± 9****</td>
<td>22·71 ± 0·53***</td>
</tr>
<tr>
<td>Recovery 12:63 ± 7·49</td>
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</tbody>
</table>

HF, LF = high, low frequency power; SBP = systolic blood pressure; AT = anaerobic threshold. *P<0·05; **P<0·01; ***P<0·001 vs baseline (paired t-test).

Statistical analysis

The results are given as means ± SEM. Due to their skewed distribution, the high frequency oscillations were used for statistical analysis after natural logarithmic transformation. A repeated measures analysis of variance model was used to assess overall changes during the various steps of the protocol in the whole group. Two-factor mixed design, and repeated measures on one-factor analysis of variance were applied to test differences between the different steps of the exercise test. When data were significant at P<0·05 a multiple t-test was used to evaluate the differences between the different steps. Simple and multiple linear regression analyses were used to assess the relationship between respiratory sinus arrhythmia and cardiovascular and respiratory variables.

Results

Cardiac and respiratory parameters

These were all within the normal range, although heart rate was lower in control subjects than in heart transplanted subjects. Low frequency oscillations and high frequency respiratory-synchronous oscillations were present on the R-R interval spectrum of all subjects.

Exercise

Respiratory parameters

On initiation of exercise, VO₂ increased suddenly, and the subjects reached the anaerobic threshold at 125-150 W.

Cardiac parameters

R-R interval and R-R standard deviation decreased on initiation of exercise and showed a significant increase during the recovery phase. In a similar way, low frequency and respiratory-related oscillations decreased significantly during exercise and increased in the recovery phase. Systolic blood pressure increased throughout the exercise.

Control subjects

The results are shown in Table 2. All subjects reached the anaerobic threshold, and the exercise test was stopped because of leg fatigue or exhaustion.

Heart transplanted patients

The results are shown in Table 3. The patients studied started exercise with a heart rate higher than that of control subjects (99 ± 2 vs 70 ± beats. min⁻¹).
Table 3 Exercise results — heart transplanted subjects

<table>
<thead>
<tr>
<th>Heart rate (beats min⁻¹)</th>
<th>R-R mean (ms)</th>
<th>R-R SD (ms)</th>
<th>HF (ln ms²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>99 ± 2</td>
<td>620 ± 16</td>
<td>5.1 ± 0.5</td>
</tr>
<tr>
<td>25s</td>
<td>105 ± 2*</td>
<td>585 ± 15**</td>
<td>5.7 ± 0.5</td>
</tr>
<tr>
<td>25e</td>
<td>109 ± 2**</td>
<td>562 ± 14***</td>
<td>5.3 ± 0.4</td>
</tr>
<tr>
<td>50</td>
<td>120 ± 3***</td>
<td>507 ± 12**</td>
<td>4.9 ± 0.4</td>
</tr>
<tr>
<td>75</td>
<td>132 ± 3***</td>
<td>461 ± 13**</td>
<td>4.1 ± 0.5**</td>
</tr>
<tr>
<td>Recovery</td>
<td>123 ± 3***</td>
<td>500 ± 15***</td>
<td>3.2 ± 0.3**</td>
</tr>
</tbody>
</table>

SBP (mmHg) VO₂ (ml kg⁻¹ min⁻¹) AT (VO₂/VCO₂)

| 0           | 138 ± 3   | 3.73 ± 0.14 | 0.86 ± 0.01 |
| 25s        | —         | 9.25 ± 0.43*** | —          |
| 25e        | 157 ± 4*** | 10.98 ± 0.40*** | 1.00 ± 0.01* |
| 50         | 163 ± 3*** | 13.98 ± 0.41*** | 1.12 ± 0.02*** |
| 75         | 176 ± 4*** | 16.27 ± 0.77*** | 1.16 ± 0.01*** |
| Recovery   | 136 ± 3   | 4.58 ± 0.23*  | 0.95 ± 0.02** |

*P<0.005; **P<0.01; ***P<0.001 vs baseline (paired t-test; 25s=25 W start (first 2 min), 25e=25 W end (last 2 min), SBP=systolic blood pressure; AT=anaerobic threshold.

During exercise, the heart rate increased (to 132 ± 3 beats min⁻¹; P<0.001) as did VO₂ (from 3.73 ± 0.14 to 16.27 ± 0.77 ml kg⁻¹ min⁻¹; P<0.001). All patients reached the anaerobic threshold. The exercise test was stopped because of leg fatigue or exhaustion, but induced no arrhythmia or myocardial ischaemia in any patient.

0 watt load

Respiratory parameters
These were all within the normal range.

Cardiac parameters
The heart rate was high and R-R variance low in all subjects. High frequency respiratory-synchronous oscillations were present on the R-R interval spectrum in all subjects, while low frequency oscillations were present only in five patients.

Exercise

Respiratory parameters
VO₂ increased suddenly on the initiation of exercise, but VO₂ max was significantly lower (compare Tables 2 and 3) in heart transplanted patients than in control subjects (P<0.001). Ten minutes after the exercise was stopped, VO₂ decreased but remained significantly different from baseline. All subjects reached the anaerobic threshold at a relatively low workload (60% at 50 W, 40% at 75 W).

Cardiac parameters
The R-R interval started to decrease linearly from the initiation of exercise. During the recovery phase, it again started to increase but remained significantly lower than at baseline. R-R standard deviation increased at 25 W then started to decrease to become significantly lower than baseline at peak exercise and during recovery. In a similar way the respiratory oscillations increased significantly at the beginning and the end of the 25 W step, did not increase further during the following exercise stages, then decreased rapidly below baseline levels. The oscillations in the R-R interval recorded during exercise were not due to changes in the QRS axis, as a result of the increased ventilation. The plot of a sequence of QRS complexes (Fig. 1) shows in fact marked oscillations in QRS distance, larger than the changes in the electrical axis of the heart as a result of ventilation. Comparison of the power spectrum of the R-R interval with that of respiration clearly indicates that these oscillations were synchronous with respiration and thus were an expression of respiratory sinus arrhythmia (Fig. 2). Bivariate analysis showed a strong association between high frequency R-R interval oscillations and respiratory oscillations throughout the entire test in all subjects, thus confirming the respiratory (i.e. non-random) origin of these fluctuations. Systolic blood pressure increased to the end of exercise—remaining higher than in control subjects—and returned to resting values when exercise stopped.

Correlations
In control subjects, respiratory sinus arrhythmia was inversely correlated with VO₂ (r= -0.77, P<0.0001). In heart transplanted subjects, respiratory sinus arrhythmia was inversely correlated with heart rate (r= -0.45, P<0.0001), and showed a direct correlation with VO₂ (r= +0.21, P<0.05). Multiple regression analysis showed that a linear combination of heart rate (with negative sign) plus a ventilatory parameter (VO₂ with a positive
Figure 1 A sequence of all contiguous QRS complexes aligned by their peaks, that is, to the reference point that we use to measure the R-R interval. The QRS are almost perfectly aligned, and only minimal scattering can be ascribed to changes in the axis of the QRS or to noise. In addition, we have shown, to the right, the next QRS in the sequence. Thus, the space in between is the R-R interval and the evident displacement of the second QRS line is the effect of changes in the R-R interval. A clear sinusoidal fluctuation, synchronous with respiration, can be seen.

AR = autoregressive; a.u. = arbitrary units.

Figure 2 The tachograms of the R-R interval and respiratory signals with the respective spectra, obtained from a heart transplanted subject during 25 watts exercise. The respiratory oscillations are clearly reflected in the R-R interval tachogram and the R-R interval spectrum shows only one peak, synchronous with the respiratory peak. Therefore, at submaximal exercise well defined respiration-related R-R interval changes are present in the denervated human heart.

Low frequency components of heart rate

Control subjects

The power of R-R low frequency oscillations, like R-R standard deviation, decreased significantly from 75 W to the end of exercise and showed a tendency to increase immediately once exercise stopped. Nevertheless, the low/high frequency ratio, as an expression of sympathetic activation to the heart, increased significantly during exercise.

sign) could explain the observed changed in respiratory sinus arrhythmia during exercise. Although respiratory sinus arrhythmia measured at rest did not show a significant change with time after heart transplantation (simple regression $r=0.124$, $P=ns$), a small but significant contribution to respiratory sinus arrhythmia changes was also given by the time since transplantation (months). The overall regression equation was: $\ln$ high frequency = 6.9 - 0.044 heart rate - 0.029 donor age + 0.13, $VO_2$ - 0.025 months ($r=0.65$, $P<0.001$) (Fig. 3).
Heart rate variability in heart transplanted subjects

In eight cases an oscillatory component was present in the low frequency range (between 0.03 and 0.15 Hz) of the heart rate spectrum, that is, below the usual respiratory (or high frequency) band. When the respiratory signal spectrum was compared with that of heart rate, a concomitant peak was found in three cases who had undergone heart transplantation 21 to 34 months before, in one case at rest and in two cases during exercise (an example is shown in Fig. 4), indicating that the subjects occasionally breathed slowly. Moreover, in these cases bivariate analysis showed a strong association between low frequency R-R interval oscillations and the respiratory oscillations (Fig. 5(b)). In the remaining five cases, who had had their transplant 24 to 48 months before, low frequency R-R interval oscillations were present at rest (two cases) and at submaximal exercise (three cases), an example is shown in Fig. 6) without a concomitant peak on the respiratory spectrum. In these cases the bivariate analysis confirmed the absence of a significant coherence between the low frequency R-R interval oscillations and the respiratory oscillations (Fig. 5(a)).

Discussion

Control subjects

In control subjects, the high frequency respiratory-related oscillations of heart rate — the index of vagal activity — decreased when the exercise started as a result of the combined effect of vagal withdrawal and the decrease in heart rate variability. However, the low frequency oscillations showed no significant decrease at the beginning of exercise, but decreased as the exercise progressed. The low/high frequency ratio showed a moderate tendency to increase during the first part of the exercise test, as previously reported, in agreement with a relative increase in sympathetic tone. The interpretation of low frequency oscillations is still debated, as they are considered by some authors to be an index of sympathetic activity, while we have shown in a recent work that baroreceptor activity could also take part in their genesis. In any case, although the interpretation of low frequency and the low/high frequency ratio remains open, it was important in this study to establish that the low frequency fluctuations were not caused by breathing; in this way their autonomic origin was assured, whereas the high frequency oscillations had both autonomic and mechanical origins.

Heart transplanted subjects

As previously described, in the heart transplanted patients, ventilation increased suddenly during exercise and promptly decreased immediately after. The heart rate increased gradually from the beginning of exercise (+6 beats min⁻¹ in the first 2 min and +10 beats min⁻¹ in the last 2 min of the 25 W step). This relatively prompt increase in heart rate could have been due to different factors: a large release of catecholamines during exercise, increased sensitivity to catecholamines or to an intrinsic mechanism previously hypothesized. Discrete peaks were identified on the R-R interval spectrum of all the subjects both at rest and during exercise, showing that heart rate variability of the transplanted heart is not entirely due to casual oscillations of the R-R interval but that part of it is due to well defined non-casual oscillations. Moreover, we have confirmed that during exercise (see
Figure 4  Tachograms of the R-R interval and respiratory signals with the respective spectra, obtained from a heart transplanted subject during 25 watts exercise. (a) The sequence of breaths shows an irregular breathing pattern made up of a combination of fast breathing and deep breaths occurring at a slower rate. The R-R interval sequence also shows a combination of slow and fast changes. (b) The R-R interval and respiratory spectra show coincident peaks in the low and high frequency range, suggesting that both the slow and high frequency oscillations in R-R interval are respiration related. This hypothesis was verified and confirmed from the squared coherence analysis between the R-R interval and respiratory signal (Fig. 5).

Figure 5  Squared coherence between the R-R interval and respiration in two heart transplant subjects during physical exercise. The height of the peak represents the power of the coherence, (considered to be significant when >0.5); the frequency of the peak represents the frequency at which the two signals are coherent. In (a) (same recording as Fig. 6), the two signals were coherent at high frequency, while in (b) (same recording as Fig. 4) the two signals were coherent both at high and low frequency, showing that the low frequency oscillations on the R-R interval were respiration-related.

Fig. 1), as previously shown\textsuperscript{15}, respiratory sinus arrhythmia was not due to artifactual changes in the QRS axis, as has been hypothesized\textsuperscript{12}.

Respiratory influences on high frequency oscillations

As in control subjects, the discrete peak found in the high frequency range on the heart rate spectrum of heart transplanted patients was always concomitant with a peak on the respiratory signal spectrum, as anticipated in cases of respiratory sinus arrhythmia. Non-casual R-R interval oscillations had previously been observed at rest in a minority of heart transplanted subjects\textsuperscript{11}, and the effects of breathing patterns, deep breathing, and Valsalva and Mueller manoeuvres were studied. The presence of respiratory sinus arrhythmia at rest has thus now been confirmed in a large group of heart transplant recipients. In addition, the behaviour of respiratory sinus arrhythmia in two groups (control and heart transplanted subjects) has been studied during physical exercise. Despite the fact that few control subjects were included in the study, the data observed in this group were similar to those observed in a more numerous group\textsuperscript{19} and in our previous work\textsuperscript{13}, moreover the between-group differences were so striking as to allow for comparison. While in the control subjects respiratory sinus arrhythmia decreased from the initiation of exercise to when it ceased and increased immediately
Heart rate variability in heart transplanted subjects

AR Power spectra

Figure 6 The tachograms of the RR interval and respiratory signals with the respective spectra, obtained from a heart transplant subject during 50 watts exercise (a) the RR interval sequence shows high frequency oscillations synchronous with respiration and pronounced slow frequency oscillations. (b) the R-R interval spectrum shows two peaks, one with a relatively small area, in the high frequency range (0.049 Hz), synchronous with the respiratory peak (0.049 Hz) and one with a larger area in the slow frequency range (0.05 Hz) not synchronous with a respiratory peak. The respiratory spectrum also shows two main peaks, the most important one being in the high frequency range, also synchronous with the high frequency peak in the R-R interval spectrum and a small one at a slower frequency (0.10 Hz), but different from that of the slow frequency peak in the R-R interval spectrum.

after, as expected in cases of vagal modulation of heart rate, in heart transplanted subjects the opposite occurred: the power of the respiratory-related oscillations increased at submaximal exercise and decreased thereafter and even more rapidly after exercise. In heart transplanted subjects, respiratory sinus arrhythmia showed a significant correlation with oxygen consumption (direct) and heart rate (inverse), indicating that respiration increased respiratory sinus arrhythmia during exercise while the increase in heart rate tended to reduce it. Multiple regression analysis showed the significant contribution of both of these variables taken together. Mechanical stretching of the atrium has been shown to induce changes in the intrinsic heart rate of heart transplanted subjects soon after heart transplantation. However, only anecdotal cases of vagal reinnervation have been described in these subjects and not within 2–3 years of the operation. In addition, the fact that during exercise respiratory sinus arrhythmia in heart transplant subjects behaves differently from the vagally mediated respiratory sinus arrhythmia in control subjects, means that a neural origin of the respiratory sinus arrhythmia in the heart transplanted subjects is unlikely. Moreover, in heart transplanted subjects, stretching of the myocardium could be more important than in normal subjects, because the pericardium is open, and because of the greater increase in ventricle filling pressure during exercise. Relative hypoxia of the myocardium could also play a role. Therefore an intrinsic mechanism, i.e. atrial stretching due to respiratory-linked rapid changes in venous return, may be at least partially responsible for the observed respiratory sinus arrhythmia and it could lead to the adjustment of the cardiovascular response in transplant subjects. It is known that a slight increase in heart rate has been observed at the beginning of exercise and during mild exercise in heart transplanted subjects and dogs, even after beta-blockade.

Respiratory and non-respiratory components in low frequency oscillations

In eight cases there was an oscillatory component in the low frequency range of the heart rate spectrum. In three cases a concomitant peak was found on the respiratory spectrum, indicating that the subjects were occasionally breathing slowly. Moreover, bivariate spectral analysis confirmed that low frequency R-R interval oscillations were related to respiration. If the respiratory signal had not been analysed simultaneously with the heart rate, this could have suggested a possible sympathetic modulation of cardiac activity. Nevertheless, in five of our subjects the low frequency component observed on the heart rate spectrum was not concomitant with a low frequency peak on the respiratory spectrum, nor there was a significant association (i.e. high coherence) between these low frequency R-R interval oscillations and respiratory oscillations at the cross-spectral analysis. Thus the sympathetic origin of these oscillations cannot be ruled out, however, this should be demonstrated with more specific tests.
Effect of time since transplantation

Long after transplantation, the sympathetic system could exert more efficient control over cardiac activity, as suggested by the observed dramatic fall in plasma catecholamine levels compared to the pre-transplant state[38], followed by restored beta-mediated contractility and a positive chronotropic effect[39]. Moreover, it has been observed that mismatches occur between the donor and the recipient, due to different cardiac sizes[29] and beta receptor sensitivities[37]. Thus, if the different components of the heart interact better with time after transplantation, this could improve cardiac mechanics, thus reducing filling pressures. The presence of non-respiratory low frequency waves in subjects who had received their transplant at least 2 years before also suggests the possibility of sympathetic reinnervation[38]. These data need to be confirmed in a longitudinal study with the same subjects followed over time. Although respiratory sinus arrhythmia measured at rest did not show a significant change with time after heart transplantation, changes occurring during exercise were inversely correlated with time after surgery. In the absence of any evidence of vagal reinnervation, these data might suggest that the recipient heart is mechanically better adapted to exercise.

Conclusions

In conclusion, an intrinsic mechanism related to atrial stretching and possibly to myocardial gas changes seems a common mechanism that modulates the heart rate of the transplanted heart both at rest and during physical exercise. It could play a role in adjusting the cardiac response during exercise, contributing to the increase of heart rate and permitting better diastolic filling of the ventricles in recently transplanted subjects. Respiratory sinus arrhythmia behaved in a similar way, i.e. it did not decrease during exercise, thus ruling out the possibility of vagal reinnervation even some time after transplantation. Nevertheless, in some of the long-term heart transplanted subjects, sympathetic reinnervation could not be ruled out. Fluctuations in heart period can be investigated only through the combined analysis of the simultaneously recorded R-R interval and respiratory signals.

We gratefully acknowledge the help of Prof. Peter Sleight (Cardiac Dept. John Radcliffe Hospital, Oxford, U.K.) for his suggestions and constructive criticism.

References


