Physiology and pathophysiology of heart rate and blood pressure variability in humans: is power spectral analysis largely an index of baroreflex gain?

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1. It is often assumed that the power in the low-(around 0.10 Hz) and high-frequency (around 0.25 Hz) bands obtained by power spectral analysis of cardiovascular variables reflects vagal and sympathetic tone respectively. An alternative model attributes the low-frequency band to a resonance in the control system that is produced by the inefficiently slow time constant of the reflex response to beat-to-beat changes in blood pressure effected by the sympathetic (with or without the parasympathetic) arm(s) of the baroreflex (De Boer model).

2. We have applied the De Boer model of circulatory variability to patients with varying baroreflex sensitivity and one normal subject, and have shown that the main differences in spectral power (for both low and high frequency) between and within subjects are caused by changes in the arterial baroreflex gain, particularly for vagal control of heart rate (R-R interval) and left ventricular stroke output. We have computed the power spectrum at rest and during neck suction (to stimulate carotid baroreceptors). We stimulated the baroreceptors at two frequencies (0.1 and 0.2 Hz), which were both distinct from the controlled respiration rate (0.25 Hz), in both normal subjects and heart failure patients with either sensitive or poor baroreflex control.

3. The data broadly confirm the De Boer model. The low-frequency (0.1 Hz) peak in either R-R or blood pressure variability was spontaneously generated only if the baroreflex control of the autonomic outflow was relatively intact. With a large stimulus to the carotid baroreceptor it was possible to influence the low-frequency R-R but not low-frequency blood pressure variability. This implies that it is too simplistic to use power spectral analysis as a simple measure of autonomic balance; its underlying modulation is more complex than generally believed.

4. It may be that power spectral analysis is more a sensitive indicator of baroreflex control, particularly of vagal control, than direct evidence of autonomic balance. Of course, there is often a correlation between the gain of the reflex and the autonomic balance of vagus and sympathetic. These considerations may help our understanding of some conditions, such as exercise or heart failure, when the power spectral analysis method fails to identify increased sympathetic discharge; this failure may partly be explained by the decrease in baroreflex sensitivity which occurs in these two conditions.

INTRODUCTION

Under steady-state conditions several regularly occurring fluctuations can be seen in heart rate, blood pressure and other circulatory parameters such as skin blood flow. These cyclical oscillations are related to breathing (respiratory sinus arrhythmia at about 0.25 Hz), a roughly 10s periodicity rhythm (0.1 Hz) and much slower fluctuations related perhaps to sleep, activity and temperature control. It is often assumed that the spectral indices obtained at the frequency of respiration [high frequency (HF) around 0.25 Hz] and at the so-called low-frequency (LF, around 0.1 Hz) reflect vagal and sympathetic tone respectively [1]. The ratio of these two most studied frequencies (LF and HF) has been used to indicate the balance between sympathetic and vagal tone in differing physiological and pathophysiological states [2]. These indices cannot, of course, be direct measures of autonomic nervous tone since by their nature they can only reflect the variability and not the absolute level of the signal. These simplified descriptors are clearly not universally applicable. For example, although exercise is known (from indirect measures) to be ac-

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Abbreviations: BP, blood pressure; HF, high-frequency; LF, low-frequency; PSA, power spectral analysis; SAD, sinoaortic denervation.

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compounded by vagal withdrawal and sympathetic arousal [3, 4], the LF peak is greatly reduced or abolished by increasing exercise [5, 6]. Similarly, patients with severe cardiac failure are known to have high sympathetic tone [7] and reduced sinus arrhythmia (less vagal tone) [8]. But power spectral analysis (PSA) measures in heart failure show reduced LF [9, 10].

This paper presents possible explanations for these discrepancies and describes some preliminary and confirmatory experiments which follow from a development of the De Boer model hypothesis for the origin of the LF peak in the PSA [11]. The De Boer hypothesis is based on a mathematical model of the circulation. This model examines the interactions of the fast vagal response to baroreceptor stimulation and the slower response of the sympathetic efferent systems controlling the arterial smooth muscle. Resonance at a frequency of about 0.1 Hz can occur in such a system, which has feedback loops with different time constants. The conditions necessary to generate the oscillations shown in the LF part of the power spectrum are that (1) the sympathetic efferent systems are intact, (2) there is a functional baroreflex and (3) there is a reactive vascular system. Atropine markedly reduces the LF R–R as well as the HF R–R fluctuations in circulatory variables [12] since it removes the fast vagal response which accentuates the resonance caused by the slow sympathetic response to baroreceptor stimulation. The De Boer hypothesis could also explain why conditions which are associated with a reduction in gain of the arterial baroreflex control (such as exercise or heart failure) [8, 13, 14] are also associated with diminution of the LF peak, despite other good evidence of increased sympathetic tone [7, 15, 16].

To test the De Boer hypothesis we have carried out preliminary studies on one young normal subject with good baroreflexes and on patients who were under assessment for cardiac transplantation, whose sympathetic drive is high.

**METHODS**

We have considered as examples (a) a normal subject (b) a patient with heart failure who had an unusually well-preserved baroreflex control of R–R (phenylephrine slope = 11 ms/mmHg) [17] and (c) another patient who initially had a poor baroreflex (slope 1.9 ms/mmHg), but who (after 6 months) improved considerably, and his baroreflex slope rose (9.7 ms/mmHg) (see Table 1 for details). The normal subject was young and showed good heart rate variability with respiration; for these reasons his baroreflex response to injected phenylephrine was not tested.

All subjects gave informed consent; ethical permission for the baroreflex studies was granted by the Fondazione Clinica del Lavoro.

Under conditions of controlled respiration at 15/min (0.25 Hz), we stimulated the carotid baroreceptors by neck suction at each of two frequencies (0.1 and 0.2 Hz) which were different from the respiratory frequency. In this way it was possible to detect the effect of pure baroreceptor stimuli on LF and HF power in the PSA, as distinct from the power in the peaks related to respiration and its central entrainment. The three subjects underwent the same protocol and gave informed consent to the investigation. The subjects remained supine during the tests. The ECG and respiration were both measured using an electrical impedance spirometer [6] and non-invasive blood pressure by the Finapres device [18] (Ohmeda model 2300, Englewood, U.S.A.). Neck suction was performed with a neck suction chamber [19] connected to a vacuum cleaner whose power supply could be continuously varied by a servo-control system built in our laboratory, modulated by a function generator (Kron-Hite, model 5200. Avon, U.S.A.). As a consequence, the neck suction could be generated with a predetermined signal shape and frequency and pressure swing. After a 4-min baseline recording, sinusoidal neck suction (30 mmHg) was then generated for 2-min sequences in random order at the two test frequencies to test the ability of the baroreceptors to generate a respiratory sinus arrhythmia-like stimulus on the R–R interval (by modulation of the vagel efferent activity). The respiration rate was maintained at 0.25 Hz (15 breaths/min) by voice or signal; this also prevented hyperventilation. The procedure was repeated, with good agreement between the two values. The signals were digitized on-line at 500 Hz per channel and analysed by autoregressive PSA [1, 6]. The autoregressive model order was 12–14.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Aetiology</th>
<th>NYHA class</th>
<th>LVEDD (mm)</th>
<th>LVEF (%)</th>
<th>CI (l min m⁻²)</th>
<th>PCP (mmHg)</th>
<th>VO₂max/kg</th>
<th>Slope (ms/mmHg)</th>
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<td>28</td>
<td>2.26</td>
<td>21</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
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<td>Ischaemic</td>
<td>II</td>
<td>66</td>
<td>22</td>
<td>1.87</td>
<td>29</td>
<td>10</td>
<td>1.9</td>
</tr>
<tr>
<td>CHF2b 53</td>
<td>Ischaemic</td>
<td>II</td>
<td>64</td>
<td>22</td>
<td>1.80</td>
<td>8</td>
<td>18</td>
<td>9.7</td>
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**Table I. General characteristics and baroreflex sensitivity slopes (BRS) of the two congestive heart failure patients.**

Patient 1 had an unusually normal baroreflex slope. Patient 2 was studied before (CHF2a) and after compensation and clinical improvement (CHF2b), when the BRS was markedly increased. NYHA, New York Heart Association; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; CI, cardiac index; PCP, pulmonary capillary pressure.
Baroreflex modulation of heart rate and blood pressure variability

Normal subject

CHF patient 1

CHF patient 2 record a

CHF patient 2 record b

Systolic pressure

Diastolic pressure

Fig. 1. Power spectral density of (a) tachogram, (b) systogram and (c) diastogram during controlled respiration (0.25 Hz) in a normal subject and two patients with congestive heart failure with good (patient 1) and poor (patient 2 record a) baroreceptor reflexes. The magnitude of R-R variability (see Table 2) decreases from normal subject to patients and, among patients, with increasing severity of the disease. After clinical improvement patient 2 showed an increase in heart rate variability (record b) related to an increase in baroreceptor responsiveness.

RESULTS

The PSA results can be seen in Figs. 1–3. It is important to note that the scales for these figures differ markedly because the size of the variability in any parameter is very much greater in the normal subject than in the patients.

Controlled respiration

First (as stated above) note from Table 2 that during controlled respiration alone (basal condition with no neck suction) the total power of R-R variability in the normal subject was greater than in the two heart failure subjects. The power of the R-R variability at both 0.25 Hz (HF) and 0.1 Hz (LF) is greatly reduced in the heart failure subjects (Fig. 1), particularly in the subject (2a) in whom there was initially poor baroreflex control of R-R interval. With improvement subject 2 increased total power fivefold and HF power 10-fold (see Table 2). The differences in the generally low blood pressure variability between the normal and the two heart failure patients and between the poor and improved (2a and 2b) records for patient 2 are much less striking (see Table 2).

Neck suction at 0.1 Hz

With 30 mm Hz sinusoidal neck suction at 0.1 Hz the normal subject and heart failure patient 1 (good reflexes) behave very similarly (Fig. 2, Table 3). The previously dominant respiratory peak at 0.25 Hz is now much smaller in comparison with the baseline because the strong stimulus to the baroreceptors at 0.1 Hz dominates the power spectrum, so that on the scale of the diagram shown the 0.25-Hz peak may not be appreciated at all (it can be seen on an expanded scale not shown). Note also that the neck suction entrained peak is present in all three parameters (R-R, systolic pressure, diastolic pressure) in the normal subject and in the subject with good reflexes (patient 1) but not in patient 2 (first recording) except in R-R; in this patient, after improvement, R-R variability increased five fold. Similarly, patient 2 showed an increase in blood pressure (BP) variability with improvement in his circulatory state. In general, the LF power at 0.1 Hz is related to the amount of the baroreflex gain differences (see Table 3).

Neck suction at 0.2 Hz

In the normal subject and in patient 1 (good baroreflex) a dominant peak is seen at 0.2 Hz (Fig. 3, Table 4). The respiratory peak at 0.25 Hz is seen in most records in the normal subject and in patient 1, except for the R-R spectrum in the normal subject. Here the huge power of the neck suction-induced 0.2-Hz peak dominates the graph, and
0.25 Hz power in the R–R spectrum was only seen on an expanded scale (not shown, but see Table 4). Patient 2 (record a) shows a very low power at 0.2 Hz and then only on the R–R spectrum. This low R–R variability again increased four fold with clinical improvement. In patient 2, record b, the respiratory peak (0.25 Hz) likewise shows a very low power compared with that of patient 1. These peaks seen at 0.25 Hz on record 2a are likely to be mechanically induced, not reflex [20]. In addition, note the appearance of a new peak on all three parameters in patient 1 at 0.06 Hz (Fig. 3). At first sight this might be thought to be a harmonic of the neck suction stimulus, but it is not (neck suction was at 0.2 Hz). On further examination of this peak in patient 1 we found a striking fluctuation in the tidal volume of the controlled breathing. The periodicity of this waxing and waning of the tidal volume was at 0.7 Hz and highly coherent with the peak in the circulatory variables on PSA. The reason for this sinusoidal fluctuation in tidal volume is not clear. Again note (Table 4) that the 0.2 Hz power in the R–R spectrum paralleled the baroreflex gain within (subject 2) and between subjects.

**DISCUSSION**

We believe that these studies confirm the De Boer model [11], which implies that the LF peak in PSA is normally produced by variation in sympathetic discharge produced by resonant interaction between the fast vagal and slow sympathetic response to baroreceptor stimulation. These parallels between variability and baroreflex gain are best seen for R–R, but are also seen for the BP variability at 0.1 Hz. At 0.2 Hz the relation is still present for R–R but not for BP, perhaps mainly because the vascular smooth muscle cannot respond to these frequencies. We have shown that in two heart failure patients (in whom the sympathetic tone is expected to be high) an increase in the LF peak is only seen on all three circulatory parameters we recorded (R–R, systolic blood pressure and diastolic blood pressure) when: (1) the baroreflex is relatively intact (in patient 1 and in patient 2 after improvement, 2b) and (2) the rate of stimulation is slow enough (0.1 Hz) for the sympathetic efferent system to be able to respond. At higher rates of stimulation (e.g. 0.2 Hz) the vagal efferents are still able to follow and so influence the fluctuations in R–R (via the sinus node) and systolic pressure (via change in left stroke output [21]), but the sympathetic (vascular) efferents cannot follow and so there is no discernible effect on the spectra seen in the diastolic pressure.

On this basis we suggest that the baroreflex reduction seen in most patients with heart failure has altered the absolute sympathetic–vagal balance and simultaneously has changed the LF/HF ratio.

Fig. 2. Power spectral density of (a) tachogram, (b) systogram and (c) diastogram during neck suction at 0.1 Hz ( ) in a normal subject and two patients with congestive heart failure with good (patient 1) and poor (patient 2 record a) baroreceptor reflexes. Record 2b refers to patient 2 after compensation and clinical improvement. It is important to note that the scales for this Figure differ from those of Fig. 1 due to the much greater variability generated by the neck stimulus than by controlled respiration. The variability at the respiratory frequency of 0.25 Hz does not show on this scale but could be seen on expanded scale, e.g. see Table 4.
Baroreflex modulation of heart rate and blood pressure variability

As we have seen above, the LF power (and hence the LF/HF ratio) is determined by and requires the baroreflex in order to generate the sympathetic oscillation at about 0.1 Hz. Stated differently, the PSA patterns may be primarily a sensitive descriptor of the circulatory reflexes, and it may be that these reflexes then 'set' the absolute level of parasympathetic and sympathetic tone.

The examples shown in this study explain why PSA is unable to identify the high level of sympathetic tone which has been demonstrated in heart failure. Other measures, particularly direct recording of sympathetic nerve activity, may be more appropriate [22] to identify such high tone.

It may be argued that the figures in Tables 2, 3 and 4 show no consistent or convincing correlation between the baroreflex gain and blood pressure variability. However, we should not be surprised that in so few subjects there will be some confusion caused by noise. It is surprising that there is such a striking correlation between 0.1 Hz stimulation of the baroreceptor by neck suction and the changes in both HF and LF of the R–R spectrum. Note also that when baroreflex gain is higher less variability in BP should be expected, since fast R–R (and perhaps fast left ventricular output) changes via the vagus would be expected rapidly to buffer changes in pressure, and hence result in lower BP variability.
We have recently shown that baroreflex-induced low-frequency oscillations in pulse interval caused by a single neck suction transient (600 ms) during apnoea correlate strikingly with the time of the peak in spontaneous LF oscillation seen in an individual during normal breathing [23].

These observations in man are supported by those in animals before and after sinoaortic denervation (SAD) [1]. After SAD the power in the region of 0.1 Hz is significantly reduced for both blood pressure and pulse interval variability, compared with that with the baroreflex intact. Animal studies have also led to the conclusion that spectral analysis only quantifies the variability of a system and not the activity of its generating components [24].

In conclusion, this study indicates that PSA of circulatory variables may be an index more of the sensitivity (or gain) of the control by the baroreflex than of specific sympathetic or parasympathetic tone or the balance between one and the other. This may help explain why in some instances (such as heart failure or exercise) PSA (LF) is unable to identify increased sympathetic discharge, because the baroreflex control of vagal effects on heart rate is severely blunted in both these states.

REFERENCES


