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ORIGINAL ARTICLE

The Haemodynamic Instability Score (HIS) for assessment of cardiovascular reactivity in hypertensive and normotensive patients

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The normal response to postural challenge is characterised by maintenance of relatively stable blood pressure (BP) and heart rate (HR) after 30 sec to 30 min of head-up tilt. The objective of the present study was to determine the degree of instability of cardiovascular responses to postural challenge in normotensive and hypertensive subjects. In the initial phase of the study, two groups of age and sex-matched subjects were assessed: essential hypertension (n = 20) and healthy (n = 37). The BP and HR were recorded at 5-min intervals during the course of the 10-min supine-30-min head-up tilt test (HUTT). We categorised 'BP-change' as the difference between individual BP measurements during HUTT and the last recumbent BP value, divided by latter value. The average and standard deviation (SD) of the recorded BP changes were calculated, and BP changes were plotted along a time curve. A computerised image analyser then calculated the outline ratio (OR) and fractal dimension (FD) values for each of the curves. An identical process evaluated measurements for HR-changes. BP- and HR-changes were then converted into absolute numbers, and the average, SD, OR, and FD were calculated. A multivariate analysis was conducted, evaluating independent predictors of hypertension. Finally, an equation for the calculation of 'haemodynamic instability score' (HIS) was deduced and a cut-off between HIS of hypertensive and normotensive subjects was established. Independent predictors of the cardiovascular response to postural challenge of hypertensives (Group I) *vs* healthy (Group II) were: a.DIAST-FD, a.HR-AVG, a.HR-SD, a.HR-FD, DIAS-SD and HR-SD and HR-SD. Based on these five predictors, a linear discriminant score was computed and called the Haemodynamic Instability Score (HIS): HIS = 59.4 + (–16.6*a.DIAST-FD) + (−29.0*a.HR-AVG) + (−82.4*a.HR-SD) + (−30.1*a.HR-FD) + (−57.9*DIAS-SD) + (73.4*HR-SD) The HIS values in Group I (hypertensives) were: avg = 3.348, SD = 2.863, and 95% CI for mean = 2.008, 4.688. The HIS values in Group II (healthy) were: avg = −3.394, SD = 2.435, 95% CI for mean = −4.206, −2.582. Values of the HIS >-2.09 were generally observed in hypertensives (sensitivity 95%) and values $\leqslant-2.09$ were usually seen in the healthy (specificity 81.1%). The HIS was cross-validated in an additional group of hypertensive patients (n = 73). In the latter group, the HIS values were: avg = −0.456, SD = 4.403, 95% CI for mean = −1.506, 0.593 and 71.4% sensitivity at the proposed cut-off point. In conclusion, the HIS confers numerical expression to the degree of lability of BP and HR during postural challenge. Based on this score, a distinction between the cardiovascular reactivity of hypertensives *vs* normotensives is drawn. Possible applications of HIS are discussed.
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Introduction

Interesting questions arise directly from clinical practice. We studied patients with chronic fatigue syndrome who underwent a head-up tilt test (HUTT). Although lability of blood pressure (BP) and heart rate (HR) was perceived in practically all patients who underwent the HUTT, the familiar end-points of the test (vasodepressor reaction, cardiodepressor reaction, orthostatic hypotension, postural tachycardia syndrome) expressed these excessive changes in only half of the subjects. We therefore conducted a search for more precise parameters to detect haemodynamic instability, and found a method to express this numerically: the Haemodynamic Instability Score (HIS). The new method

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accurately distinguished the pathological BP and HR instability found in patients with chronic fatigue syndrome *vs* the 'normal instability' in healthy persons (Naschitz *et al*, personal communication). We anticipate that a similar study in hypertensive patients could expand our understanding of cardiovascular reactivity.

Cardiovascular reactivity is defined as the change in BP, HR or other haemodynamic parameters in response to physical or mental stimuli.[1] Data from clinical studies has shown that cardiovascular reactivity is relatively constant for each individual. Racial differences in reactivity have been observed, with enhanced vascular reactivity in blacks by comparison to whites. It is unclear whether increased reactivity is observed in hypertensive patients and in individuals who are at greater risk for developing hypertension.[1–3] Various methods are employed for the study of cardiovascular reactivity. Twenty-four hour ambulatory monitoring measures short- and long-term variabilities in BP and HR. In the laboratory, the cardiovascular reactivity is studied under psychical challenge, cold pressor, postural challenge, lower-body negative pressure, physical exercise, and combined mental and physical challenges.[4–6] The aim of these efforts is to measure BP and HR changes under various conditions, and compare them to baseline values, thereby determining cardiovascular reactivity. The ability of any of these methods to diagnose present and possibly predict future disease has not been convincingly demonstrated. An improved method for the assessment of cardiovascular reactivity may be useful for achievement of these goals.

Our proposed method for the measurement of cardiovascular reactivity involves computation of BP- and HR-changes during HUTT, followed by processing of the data by novel image analysis methods. The degree of BP and HR instability is then used for comparison between hypertensive and healthy subjects.

Methods

The study was approved by the institutional committee for human investigation at our hospital. The database of earlier investigations[7] was evaluated. Technicians carrying out the HUTT measurements did not know of the intention to compare between the groups; subsequent analysis of charts was done by outside investigators who were unaware of the study's intention.

Study population

In the first phase of the study, two groups of age and sex-matched subjects were compared. Group I (n = 20) included patients with mild-to-moderate essential hypertension according to criteria of the Sixth Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.[8] Group II (n = 37) included healthy subjects recruited from the hospital staff who had normal physical examination, routine laboratory tests, chest X-rays and electrocardiogram findings. In a second phase of the study, reproducibility of the results was assessed in Group III (n = 73) including patients with mild-to-moderate hypertension. The latter differed from Group I by their older age and associated illnesses (Table 1). As an addendum to the study, the cardiovascular reactivity of a group of patients (n = 30) suffering from chronic fatigue syndrome (CFS) was assessed and compared with the cardiovascular reactivity of Groups I–III patients. The CFS patients were referred from a chronic fatigue clinic for evaluation of their autonomic functions.[7] All patients met the definition of CFS,[9] had no other diagnosable medical or psychiatric cause to explain their symptoms, and were fully ambulatory. Thirty among them, who matched the age and sex distribution of Group I and II patients, were selected.

Not included in the study population were women receiving oral contraceptives or hormone replacement therapy, and patients with a history of congestive heart failure or neurologic disorders. The subjects enrolled in the study were not taking medications for at least 2 weeks before the study.

The protocol of the HUTT was based on the 10-min supine/30 min head-up tilt test as previously described.[10] Testing was conducted from 8.00 to 11.00 am, in a quiet environment, and at constant room temperature of 22–25°C. The patients maintained a regular meal schedule, but were restricted from smoking and caffeine ingestion within 6 h of the examination. Intake of food products and medications with sympathomimetic activity prior to the study was prohibited. Manual BP readings were taken by a physician certified in the BP measurement technique according to American Heart Association recommendations.[11] We favoured the mercury column sphygmomanometer (Baumanometer, standby model 0661–0250), since this is the standard non-invasive method for BP measurement, and is the most accurate for evalu-

Table 1 Clinical data of patients and controls

	Groups		
	I HT (n = 20)	*II Healthy (n = 37)*	*III HT (n = 77)*
Age years (SD)	26.8 (SD 12.1)	27.4 (SD 9.1)	52.3 (SD 12.6)
Male %	42	35	47
Ischaemic heart disease	0	0	12
Diabetes mellitis	0	0	7
Systolic BP (mm Hg)*	147.2 (16.7)	111.6 (9.8)	150.1 (17.2)
Diastolic BP (mm Hg)*	97.0 (10.4)	75.2 (5.6)	93.2 (10.6)

Values at the end of the supine phase.

ation of BP at rest[12,13] and during HUTT.[14,15] The HR measurements were recorded on an electrocardiographic monitor. The patient lay in a supine position on the tilt table, secured to the table at the chest, hips and knees with adhesive girdles. The cuff of the BP recording device was attached to the left arm, which was supported at heart level at all times during the study. Three measurements in the supine position were recorded at 5-min intervals. The table was then gently tilted head-up to an angle of 70°. The duration of the tilt was 30 min. During the initial 5 min of tilt, measurements were obtained at 1-min intervals, followed by readings every 5 min. When dizziness or faintness occurred, repeated measurements were taken at 30-sec intervals. In the event of a loss of consciousness the test was discontinued.

Parameters

The 'BP-change' and 'HR-change' were computed.

Systolic and diastolic BP-changes: These were defined as the differences between individual BP values measured during HUTT and the last recumbent BP value, and divided by the last recumbent BP value. The results is BP change, expressed as relative values by comparison to the last supine measurement, were calculated according to the following equation:

$$\text{BP change} = BP_{(n1\ldots n13)} - BP_{n3}/BP_{n3}). \quad (1)$$

The averages and SD of systolic and diastolic BP changes was calculated for each subject and labelled SYST-AVG, DIAST-AVG, SYST-SD and DIAST-SD, respectively. The BP changes were also represented graphically in time-curves. These figures were constructed in a fixed template on Microsoft Excel graphics. The frame measured two rectangles on the horizontal axis and 12 rectangles on the vertical axis. The X-axis was calibrated from 1 to 13 representing the time of measurements. The Y-axis was calibrated from 0 to 0.6 representing the values of the BP change (calculated according to Equation 1). The time-curves were depicted as continuous, thin black lines on white background. Subsequently, the time-curves were saved as tagged image file format (TIFF) for best resolution (Figure 1). The images were loaded in a computerised image analyser (Image Pro-plus 4, Media Cybernetics, USA). The length of the time-curve outlines was automatically measured. The outline ratio (OR) was calculated by dividing the length of the outline curve by the length of a straight line on the horizontal axis from 1 to 13. Evidently, time curves displaying greater amplitudes and number of oscillations translate into higher OR values. The fractal dimension (FD) of the time-curves was automatically computed using the box counting method.[16] The determined parameters were labeled SYST-OR, SYST-FD, DIAST-OR and DIAST-FD, respectively. The FD represents the 'self-similarity' in dynamic behaviour over multiple scales of time, while the OR merely measures the irregularity of the time-curves.

Absolute systolic and diastolic BP changes: These were computed by transforming positive and negative BP changes into positive values. The relative values BP changes were calculated as above. Subsequently, the average, SD, OR and FD of the absolute BP changes were calculated and labelled a.SYST-AVG, a.SYST-SD, a.SYST-OR, a.SYST-FD, a.DIAST-AVG, a.DIAST-SD, a.DIAST-OR and a.DIAST-FD (Figure 1).

Heart rate change: This was defined as the difference between successive HR values and the last recumbent HR value, and divided by the last recumbent HR value:

$$\text{HR change} = HR_{(n1\ldots n3)} - HR_{n3}/HR_{n3} \quad (2)$$

The HR changes average, SD, OR and FD were calculated and labelled HR-AVG, HR-SD, HR-OR, HR-FD.

Absolute HR changes: These were derived by the transformation of positive and negative HR change values into positive numbers. The absolute HR changes average, SD, OR and FD were calculated: a.HR-AVG, a.HR-SD, a.HR-OR, a.HR-FD.

Overall, 24 variables were defined and collectively called 'cardiovascular reactivity indices'.

Data analysis

In each group, the mean and SD of all cardiovascular reactivity indices were calculated and group comparisons were performed. Chi-square test and ANOVA followed by the Bonferroni *post hoc* test were used for the univariate analysis as appropriate. For multivariate analysis, forward stepwise discriminant analysis method was applied. A two-tailed *P*-value of 0.05 or less was accepted as statistically significant. The predictive characteristics (sensitivity, specificity and total accuracy) were calculated from the discrimihant model, using regression coefficients of the relevant independent variables (predictors) and from their 2×2 tables. Based on the fitted mathematical model, a discriminant score of the haemodynamic reactivity indices was calculated in order to distinguish between Group I hypertensives from Group II healthy subjects. Receiver characteristic curve analysis (ROC) was built using the Wilcoxon's method for the detection of the best cut-off point of the discriminant score. Subsequently, the HIS was cross-validated in Group III hypertensive patients.

Results

The tilt test was completed in all patients belonging to Groups I and II, but had to be prematurely termin-

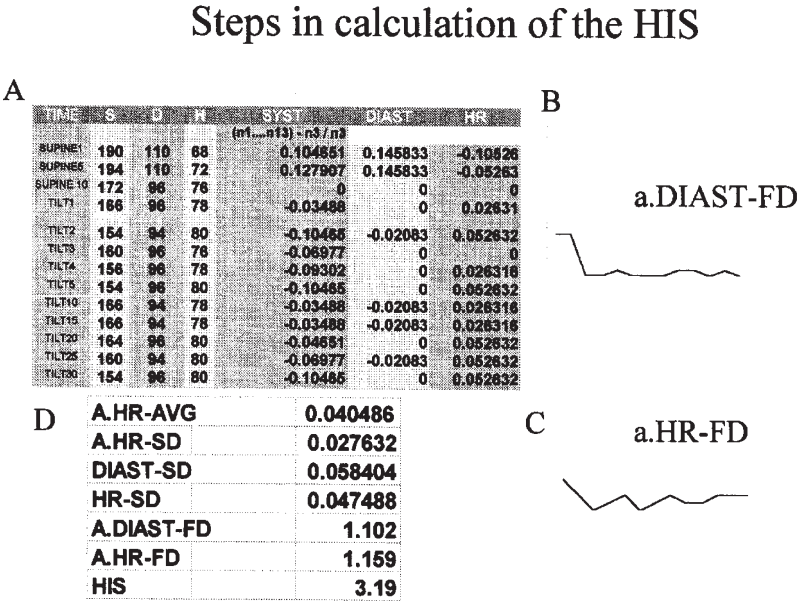

Figure 1 Calculation of cardiovascular reactivity indices. Cardiovascular reactivity indices are computed by analysing measurements taken along the HUTT. From a series of natural BP values (S and D), the BP-changes are calculated according to the equation: BP-change = $BP_{(n1\ldots n13)} - BP_{n3/n3}$ and labelled SYST and DIAST (**A**). The HR-changes are calculated similarly. From the BP- and HR-changes, the corresponding values of the absolute BP- and HR-changes are determined (labelled a.SYST and a.DIAST, not shown in Figure 1). Time-curves are then constructed (**B** and **C**). The fractal dimensions of the time-curves are calculated with a computer program. Eventually, independent predictors of the HIS are calculated (**D**) and the HIS is computed with the aid of equation 3.

ated in four patients of Group III, when postural symptoms occurred. The latter files were not included in the study.

Univariate analysis, comparing cardiovascular reactivity indices of Group I hypertensive patients with Group II normotensive subjects showed that hypertensive patients had significantly lower diastolic BP-change on HUTT by comparison to healthy subjects. This was expressed by the parameters DIAST-SD, DIAST-OR, DIAST-FD, and a.DIAST-FD. Hypertensives also had significantly lower HR-change on HUTT compared to healthy (Figure 2). In fact, Group I patients had significantly lower values

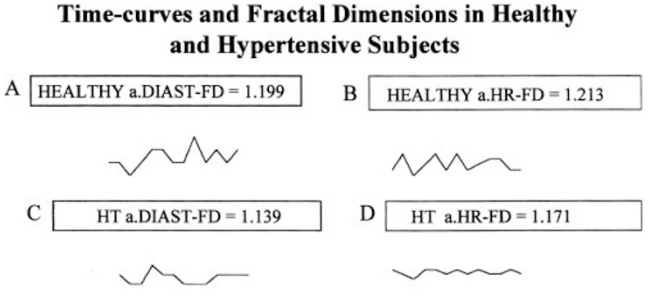

Figure 2 Typical time curves of the absolute values of diastolic BP changes (a.DIAST-FD) and HR changes (a.HR-FD). Tracings **A** and **B** were recorded in a healthy subject, while tracings **C** and **D** were recorded in a patient with moderate systolic and diastolic hypertension. The time curves in the healthy person are more irregular than those observed in the hypertensive patient, and their through-to-peak oscillations are greater. The perceptible difference between the tracings is further substantiated in the fractal dimensions.

of a.HR-AVG, a.HR-OR and a.HR-FD than Group II subjects (Table 2). Independent predictors of the cardiovascular reactivity of hypertensives (Group I) *vs* normals (Group II) during postural challenge, as determined by multivariate discriminant analysis, were: a.DIAST-FD, a.HR-AVG, a.HR-SD, a.HR-FD, DIAST-SD and HR-SD. Based on the regression coefficients (slopes and intercept) of these five predictors, a linear discriminant score was computed for each subject.[16] The obtained value was called the 'Haemodynamic Instability Score' (HIS).

$$\begin{aligned} HIS = {} & 59.4 + (-16.6*\text{a.DIAST-FD}) \\ & + (-29.0*\text{a.HR-AVG}) + (-82.4*\text{a.HR-SD}) \\ & + (-30.1*\text{a.HR-FD}) + (-57.9*\text{DIAST-SD}) \\ & + 73.4*\text{HR-SD}) \end{aligned} \quad (3)$$

The HIS values were determined for each subject according to equation 3. Subsequently, HIS group averages were calculated. The HIS values in Group I (hypertensives) were: avg = 3.348, SD = 2.863, and 95% CI for mean = 2.008, 4.688. The HIS values in Group II (healthy) were: avg = −3.394, SD = 2.435, 95% CI for mean = −4.206, −2.582. Cut-off points of the HIS were assessed, aimed at differentiating between hypertensives (Group I) and normotensives (Group II). For this purpose ROC analysis was performed. The best cut-off point was found to be −2.09. Values of the HIS $>$ −2.09 were generally observed in hypertensives (sensitivity 95%), whereas HIS values $\leqslant$ −2.09 were usually seen in healthy subjects (specificity 81.1%) (Figure 3).

Table 2 Univariate analysis of cardiovascular instability indices comparing age and sex-matched groups of hypertensives (Group I) and healthy subjects (Group II). Another, larger group of hypertensives (Group III) was intended for subsequent cross-validation of the parameters

Parameter	*Group I (HT) (n = 20) mean (SD)*	*Group II (Healthy) (n = 37) mean (SD)*	*Group III (n = 73) mean (SD)*	*P value (significance)*
SYST-AVG	−0.011 (0.043)	−0.013 (0.046)	0.024 (0.060)	NS
SYST-SD	0.044 (0.011)	0.045 (0.014)	0.051 (0.026)	NS
SYST-OR	1.128 (0.067)	1.164 (0.089)	1.138 (0.102)	NS
SYST-FD	1.103 (0.026)	1.110 (0.020)	1.097 (0.022)	0.01 (II *vs* III)
DIAST-AVG	0.030 (0.062)	0.047 (0.078)	0.006 (0.075)	0.03 (II *vs* III)
DIAST-SD	0.044 (0.018)	0.066 (0.019)	0.057 (0.038)	0.03 (I *vs* II)
DIAST-OR	1.125 (0.098)	1.309 (0.265)	1.179 (0.118)	0.0001 (I *vs* II, II *vs* III)
DIAST-FD	1.112 (0.026)	1.148 (0.041)	1.107 (0.027)	<0.0001 (I *vs* II, II *vs* III)
HR-AVG	0.072 (0.117)	0.098 (0.111)	0.049 (0.075)	0.03 (II *vs* III)
HR-SD	0.073 (0.056)	0.082 (0.041)	0.057 (0.037)	0.02 (II *vs* III)
HR-OR	1.292 (0.293)	1.317 (0.239)	1.202 (0.039)	NS
HR-FD	1.125 (0.051)	1.141 (0.035)	1.113 (0.031)	0.004 (II *vs* III)
a.SYST-AVG	0.047 (0.020)	0.053 (0.031)	0.060 (0.039)	NS
a.SYST-SD	0.034 (0.011)	0.044 (0.036)	0.041 (0.022)	NS
a.SYST-OR	1.327 (0.177)	1.484 (0.210)	1.363 (0.263)	NS
a.SYST-FD	1.153 (0.049)	1.174 (0.045)	1.152 (0.072)	NS
a.DIAST-AVG	0.057 (0.044)	0.074 (0.040)	0.066 (0.046)	NS
a.DIAST-SD	0.038 (0.019)	0.055 (0.015)	0.049 (0.035)	NS
a.DIAST-OR	1.381 (0.265)	1.794 (0.362)	1.303 (0.142)	NS
a.DIAST-FD	1.156 (0.050)	1.217 (0.057)	1.154 (0.002)	<0.0001 (I *vs* II, II *vs* III)
a.HR-AVG	0.064 (0.037)	0.106 (0.063)	0.072 (0.061)	0.02 (I *vs* II)
a.HR-SD	0.046 (0.029)	0.065 (0.030)	0.050 (0.035)	NS
a.HR-OR	1.505 (0.417)	1.901 (0.507)	1.537 (0.581)	0.003 (I *vs* II, II *vs* III)
a.HR-FD	1.131 (0.052)	1.203 (0.061)	1.162 (0.046)	<0.0001 (I *vs* II, I *vs* III, II *vs* III)

SYST, systolic BP-differences (mm Hg); OR, outline ratio; FD, fractal dimension; DIAST, diastolic BP-differences (mm Hg); HR, HR changes (beats/min). a., absolute values. Statistical analysis uses the ANOVA test followed by the Bonferroni *post hoc* test.

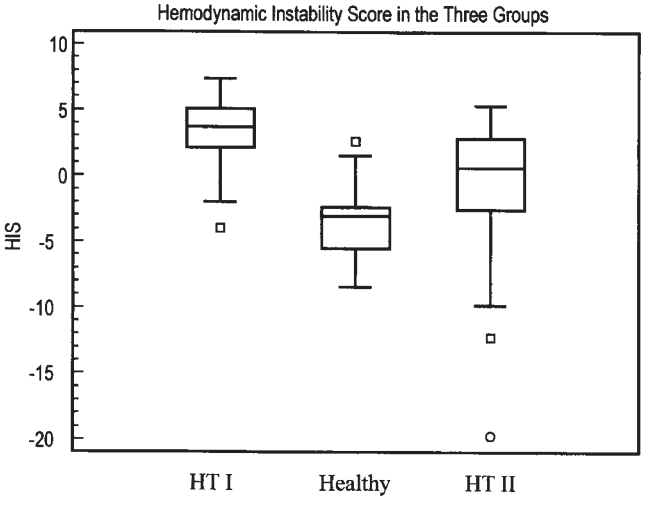

Figure 3 HIS values in the three groups of patients. At cut-off point = −2.09, the HIS of hypertensive patients is clearly separated from HIS of normotensive subjects. HT I (Group I hypertensive patients), HT II (Group II hypertensive patients).

The sensitivity of the cardiovascular reactivity indices and of the chosen HIS cut-off point at −2.09 were cross-validated in an additional group of hypertensive patients (Group III, $n = 73$). Between the two groups of hypertensives, all parameters, except for a.HR-FD, were similar (Table 2). The HIS values in Group III were: avg = −0.456, SD = 4.403, and 95% CI for mean = −1.506, 0.593 (Figure 3), and the HIS was > -2.09 in 52 instances (specificity = 81.1% and sensitivity = 71.4%).

Outside the immediate scope of our study, the HIS values of a group of CFS patients was determined with the aid of equation 3. The HIS values in CFS patients were: avg = −7.274, SD = 9.062, and 95% CI for mean = −11.016, −3.546. The values observed in the CFS group were distinctly different from HIS values in each of the hypertensive and healthy study Groups I–III ($P < 0.0001$).

Discussion

The proposed HIS of this study confers numerical expression to the degree of lability of BP and HR during postural challenge. Based on this score, a distinction between the cardiovascular reactivity of hypertensives *vs* other study populations is drawn. In comparisons of BP and HR instabilities between the groups, hypertensives were the least unstable, healthy patients had greater instability, and CFS subjects were excessively labile.

The use of the tilt table to induce postural changes in BP and HR has been widely accepted for the evaluation of syncope, and has also been applied to studies of hypertension.[10,17–20] When a normal adult stands upright, 500–700 ml of blood are pooled in the legs, reducing cardiac output and arterial pressure. The fall in pressure activates baroreceptors,

which then increase sympathetic outflow and inhibit parasympathetic activity, leading to vasoconstriction, increased heart rate and increased myocardial contractility. Humoral responses include the enhanced release of noradrenaline and subsequent secretion of antidiuretic hormone, renin, aldosterone, vasopressin, cortisone, and endothelin, and reduced secretion of atrial natriuretic factor.[21] During the initial 30 sec of tilting, an instability of the heart rate, BP, stroke volume and cardiac output is produced.[22] This is followed at 30 sec to 30 min by a stabilised response, characterised by modest haemodynamic changes. During the stabilised response to head-up tilt, a healthy young subject typically exhibits a 10–15% increase in diastolic BP, but no significant changes in the systolic BP.[17,22] The healthy elderly subject exhibits a more attenuated change in BP during the stabilised response to tilt.[23] Thus, 'instability' differs from 'variability' in that the latter refers to beat-to-beat periodicities of HR and BP,[24] while instability measures change over longer intervals.

In our study, the simplest measure of BP instability is the 'BP-change'. BP-changes were defined as the differences between individual BP values measured during HUTT and the last recumbent BP value, and divided by the last recumbent BP value. Likewise, the simplest measure of HR instability is the 'HR-change,' which is calculated in a similar fashion. Thus, BP-change was corrected with respect to BP measurements at baseline, enabling a direct comparison of values obtained for hypertensives and normotensives. Likewise, the correction of HR-change with respect to baseline HR values justified comparisons of subjects who had bradycardia or tachycardia at baseline. In this respect, the method we utilise differs from other studies, which have mainly analysed genuine BP and HR values,[2,25–27] and not their changes. Based on these primary measures of BP and HR instability, an additional set of 24 more complex parameters was computed. These parameters are the average, SD, OR and FD of the BP and HR changes, collectively called cardiovascular reactivity indices. The correlative value of these 24 cardiovascular reactivity indices with hypertension was assessed by univariate analysis. The disadvantage of univariate analysis is that it does not take into account the interdependence between the various parameters, when analysing their association with the outcome. This problem is specifically addressed by adjustments made by multivariate analysis. The independent predictors of cardiovascular reactivity in hypertensives *vs* normals were determined by multivariate analysis, and then utilised to compute equation 3, which was used for the calculation the HIS. Thus, the 24 cardiovascular reactivity indices are given expression within a single value, the HIS.

We used computer-assisted image analysis for processing of the tracings. With the availability of high speed computers and high resolution graphical displays, computed assisted image analysis has gained credit in evaluation of microscopic tissue specimen, radionuclear medicine, computerised tomography and inter-beat dynamics of HR and BP.[6,28] In our study, computer analysis was utilised to calculate the OR of the time curves, taking into account the amplitude and length measurements of the tracings. A greater amplitude and number of oscillations translate into a higher OR value. In hypertensives, the OR of the diastolic BP and diastolic HR were significantly smaller than the OR of the corresponding variables in normotensives.

While OR reflects irregularity, FD represents a 'self-similarity' in dynamic behaviour over multiple scales of time. The mathematician Benoit Mandelbrot introduced the term fractal, which describes a peculiar distribution of points in space or time.[29] The word is derived from the Latin *fractus* meaning fragmented, and fractal structure is characterised by the similarity of an object's smaller fragments to its larger ones, over a broad range of scales. Fractal measurements differ from measurements used in regular Euclidean geometry. Accordingly, OR and FD are expected to differ with respect to one another, because OR is based on Euclidean dimensions, whereas FD utilises a fractal structure. In our results, the OR and FD did, in fact, contribute in distinct ways to the calculation of HIS. In arterial hypertension, the FD of HR variability is greater than that of BP variability.[30] This observation is also supported by the present study, in which multivariate analysis shows the superior predictive value of a.HR-FD over BP-FD for hypertension. In addition, FD proves to be a more significant factor than OR for prediction of cardiovascular reactivity to postural challenge in hypertensives.

The data analysed by fractal analysis in our study differs from that presented by previous research. In our study, BP- and HR-changes were divided by baseline values. Previous studies have only analysed genuine BP and HR values. We chose to record BP and HR every 5 min, or whenever symptoms of instability presented, because this is the most accurate method for detecting clinically relevant events.[22] Other authors recorded beat-to-beat HR and BP changes, and their corresponding frequency spectra. The non-invasive beat-to-beat Finapres BP measurement device does not meet the accuracy requirements of the British Hypertension Society.[31] Furthermore, these measurements have little correlation with symptoms of haemodynamic instability.[6] FDs derived from beat-to-beat BP measurements[32–34] cannot be directly compared with FDs derived from manual BP measurements taken at 5-min intervals.

The HUTT is administered conveniently, with less than 5% dropout rate among hypertensive patients because of orthostatic symptoms.[35] It does not interfere with cardiac and haemodynamic monitoring. Its use is not restricted by cultural constraints and it is applicable to a wide range of populations. While performing a HUTT is time consuming, the

calculation of HIS is expeditious. There are many accessible and reasonably priced computer programs that can perform a fractal analysis in 1 minute's time. After the BP and HR measurements are completed, the FDs are calculated by a program as described above, and then plugged into our equation to instantly compute the HIS.

There are limitations to our study. First, the HUTT uses artificial stimuli that are not encountered in everyday life. Second, the HUTT assesses acute challenges lasting for 40 min. Third, a variety of factors may influence cardiovascular responses to stress tests including anaerobic fitness, the menstrual cycle, alcohol intake and smoking.[36] These factors have not been addressed in the present study. Fourth, HIS measurements have not been compared with ambulatory monitoring and with other laboratory methods for evaluation of the cardiovascular reactivity.

HIS values > -2.09 are strongly associated with hypertension. This measure is demonstrated in Group I (sensitivity = 95%), which serves as the hypertensive 'training' group, and in Group III (sensitivity = 71.4%), the 'test' group of hypertensives. Although the two groups of hypertensive patients differed in the subjects' ages and associated diseases, their HIS values remained reasonably similar. The specificity of HIS > -2.09 in hypertensive patients is 81.1%. This same cut-off point differentiates hypertensives from healthy subjects, as well as from CFS patients.

The HIS in healthy persons outlines the limits of 'normal cardiovascular instability.' By comparison to the balance of the normal cardiovascular instability, hypertensives demonstrate a pathological stability of their BP and HR measurements, and CFS patients illustrate the other extreme, displaying an excessive lability of these measures. It has been claimed that increased reactivity is observed in hypertensive patients and in individuals who are at greater risk for developing hypertension.[37] Data in the recent literature is not consistent with this claim, asserting that an increased reactivity in the laboratory, under contrived stress settings, does not necessarily correlate with hypertension in daily life.[26] The unexpected results of another study show that individuals with high trait anxiety demonstrate reduced cardiovascular reactivity while those with low trait anxiety demonstrate increased reactivity.[25] In addition, the response of systolic BP to orthostatic challenge is highly variable.[2] This data contradicts the previously accepted concept of cardiovascular hyperreactivity in hypertensives, and indirectly supports our findings that show a pathological stability of BP and HR in these patients.

There is no agreement as to the best method of assessment for cardiovascular reactivity. A method that could be used to diagnose or predict the emergence of a disease would be the most useful test of cardiovascular reactivity. This is the purpose of the described method, using the HIS. In our clinic, the HIS is being utilised to support the clinical diagnosis of CFS. We hope that the HIS can be used for monitoring changes in cardiovascular reactivity of hypertensive patients who receive BP lowering medications. Likewise, changes in cardiovascular reactivity of postural hypotension patients can be followed with the aid of the HIS, while treatment with sympathomymetic agents is provided.

In conclusion, the HIS differs from other methods that evaluate cardiovascular reactivity by giving emphasis to the magnitude of lability and to fractality of cardiovascular responses. Since HIS discriminates between diseased and healthy populations, it may conceivably be used for the diagnosis of disease states that are characterised by haemodynamic instability.

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