**Research Paper**

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# Left-insular cortex lesions perturb cardiac autonomic tone in humans

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The insular cortex is involved in cardiac regulation. The left insula is predominantly responsible for parasympathetic cardiovascular effects. Damage to this area could shift cardiovascular balance towards increased basal sympathetic tone (a pro-arrhythmic condition) and contribute to the excess cardiac mortality following stroke. Acute left insular stroke increased basal cardiac sympathetic tone and was associated with a decrease in randomness of heart rate variability. In addition, phase relationships between heart rate and blood pressure were disturbed, implying a disruption of oscillators involved in cardiovascular control. The insula appears to be involved in human heart rate regulation and damage to it may encourage a pro-arrhythmic state.

Keywords: cardiac arrhythmias; sudden cardiac death; sympathetic and parasympathetic cardiac tone

## Introduction

Stroke has an associated annual cardiac mortality of 5–10% representing the commonest cause of death in this condition.[1,2] ECG repolarisation changes and cardiac arrhythmias commonly occur after stroke.[3] Accumulated evidence implies that this excess cardiac mortality may not be solely explicable by concomitant coronary artery disease.[3] For example, subarachnoid hemorrhage is accompanied by malignant ventricular arrhythmias (including torsade des pointes) in over 50% of cases, yet autopsy often fails to reveal any evidence of coronary atheroma.[3] Recent pre-mortem studies have shown that such patients demonstrate a marked reduction of left ventricular contractility when repolarisation abnormalities are present in the ECG.[4] This occurs in the absence of arteriographically demonstrable coronary atherosclerotic stenosis or coronary vasospasm.[4] Such evidence strongly implicates the central nervous system in the generation of cardiac arrhythmias under appropriate circumstances.

It has been known that the brain can provoke cardiac arrhythmias since the beginning of the century. Goodman Levy demonstrated that the ventricular tachycardias induced by chloroform, which accounted for so many deaths during the first world war, were not due to a direct cardiac effect but were secondary to increased sympathetic activity.[5,6] A few years later, Beattie and colleagues showed that this was a consequence of activity of chloroform on hypothalamic regions.[7] Using tract tracing techniques, a pathway was implicated which descended from the hypothalamus to the intermediolateral regions of the spinal grey matter from which the sympathetic preganglionic fibers arise.

Recently the insular cortex has been implicated in the control of cardiac rate and rhythm. This area lies beneath the fronto-parietal operculum and the superior temporal plane. It is closely inter-connected with the limbic system and contains a site of visceral representation and blood pressure control.[8] It is therefore probably involved in emotional perception and integration and could mediate interrelationships between stress and cardiac autonomic tone. We recently demonstrated that phasic microstimulation (using very small constant current applications) of the rat insular cortex linked to the R wave of the ECG produced tachycardia or bradycardia responses without accompanying changes in blood pressure or respiration.[9] In addition, prolonged stimulation in this area generated progressive degrees of heart block, increased plasma norepinephrine levels and provoked death in asystole.[10] Accompanying cardiac structural changes included myocytolysis and subendocardial hemorrhages in the vicinity of the origin of the bundle of His.[10] Such changes suggest augmented cardiac sympathetic neural activity.[11,12]

In humans, we demonstrated that stimulation of the right anterior insular cortex most frequently resulted in sympathetic-derived cardiovascular responses (increased blood pressure and heart rate) whereas left insular stimulation resulted in more frequent parasympathetic effects (bradycardia).[13] These findings further extend the observations of Zamrini and colleagues who showed that infusion of a barbiturate (anesthetising the ipsilateral cortex) into the human left common carotid artery produced tachycardia, whereas infusion into the right common carotid artery generated bradycardia.[14] It was suggested there-

 

fore, that lesions of the left insular cortex might shift cardiac autonomic tone towards sympathetic predominance, a condition which has been thought to produce a pro-arrhythmic state.[15,16] To investigate this possibility we recruited patients with left insular lesions and applied non-invasive assessment of both deterministic and random elements of heart rate variability. In the frequency domain we utilised standard methods of power spectral analysis (FFT). This results in several peaks. The high frequency (HF) region of the fast Fourier transform (FFT) of heart rate (≈ 0.2 Hz) is thought to represent the oscillatory influence of respiratory drive on heart rate variability.[17] Conversely, the lower frequency (LF) component (≈ 0.1 Hz) represents predominantly cardiac sympathetic influences, but also parasympathetic and possibly other components.[17] However, evidence such as the broad band nature of the HRV spectrum, and its inverse fall-off with frequency, suggests that HRV may be a complex signal which cannot be fully decomposed into the sinusoidal components of spectral analysis.[18–20] It has been suggested that heart rate variability represents chaotic determinism, and that its attractor may be characterised by the correlation dimension.[18,21,22] More recently, a view has been expressed that HRV does not exhibit low-dimensional chaos, yet nonetheless appears to contain an element of non-linear determinism.[23,24] We therefore applied two new measures of complexity which are dependent on neither determinism nor on chaos: approximate entropy[25,26] and $\psi^2$, a statistical measure never previously applied to physiological data.[27] Portions of this work have appeared in abstract form.[28,29]

## Subjects and methods

Seven patients (mean age 54.5 ± 16.5 years) with lesions mainly confined to the left insular cortex were sequentially recruited into the study over an 18-month period. Lesion location was confirmed by MRI. Six of these patients had suffered an acute stroke and were investigated within a mean of two days of stroke onset and one had a newly-diagnosed cerebral tumor confined to this area. A representative MRI is shown in Figure 1. Three of these patients developed new ECG changes (determined by lack of changes on previous, pre-morbid ECG recordings) an example of which is shown in Figure 2. None of these patients was known to have interfering conditions such as previous stroke, diabetes, or to be receiving medications which could interfere with non-invasive assessments of cardiac autonomic tone (such as beta blockers). Two of the patients suffered from hypertension and were treated with a calcium channel antagonist. This medication does not alter heart rate variability. Seventeen individuals (mean age 50.2 ± 20.1 years) without history or clinical evidence of ischemic heart disease, structural neurological disease, hypertension

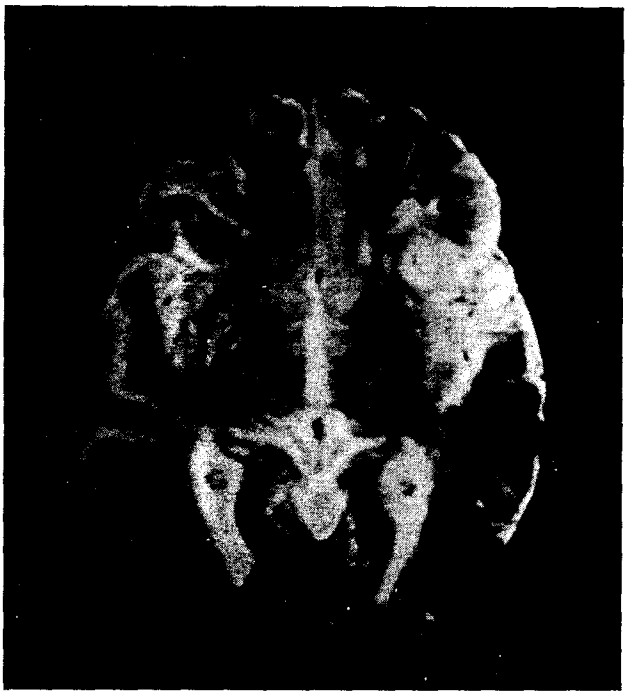

Figure 1. MRI of patient with a lesion principally confined to the left insular cortex

or medication treatment were recruited from the staff and out-patient clinics and served as a control group.

To avoid circadian influences on heart rate regulation, all patients and controls were investigated at the same time of day (mid-afternoon) using a computerised platform.[30] Data were acquired with the patient lying quietly supine for 60–80 min. Blood pressure was obtained non-invasively using a Finapres 2350 device (Ohmeda Scientific, Louisville, CO, USA); the inflatable monitoring cuff was applied to the middle finger of the right hand in most cases, except where there was peripheral vascular disease or an in-dwelling catheter. In these cases the contralateral thumb was selected for measurement. The Finapres is reliable and accurate when compared to intra-arterial pressure recording.[31] The impedance respiration signal was recorded using a Hewlett Packard 78212D monitor (Hewlett Packard, Boise, ID, USA) through two electrodes placed on opposite sides of the thorax at the mid rib-cage level. The reference ground electrode was collocated with the ECG ground electrode. The ECG signal was acquired in the lead II configuration using a Hewlett Packard 78353B monitor. The signals were digitised using a DAS 1602 A/D acquisition board (Keithley Instruments, Rochester, NY, USA) and sampled at 500 Hz. The resultant digitised data were stored on a Bernouilli disc and archived using a Panasonic optical disk drive LF 7010 (Panasonic, Secaucus, NJ, USA). Patients were monitored while supine in a quiet isolated environment, while breathing regularly. Regular breathing was chosen as heart rate variability data acquired under these circumstances shows less age dependency than metronome-induced breathing.[32] An acquisition and analysis program was written using ASYST soft-

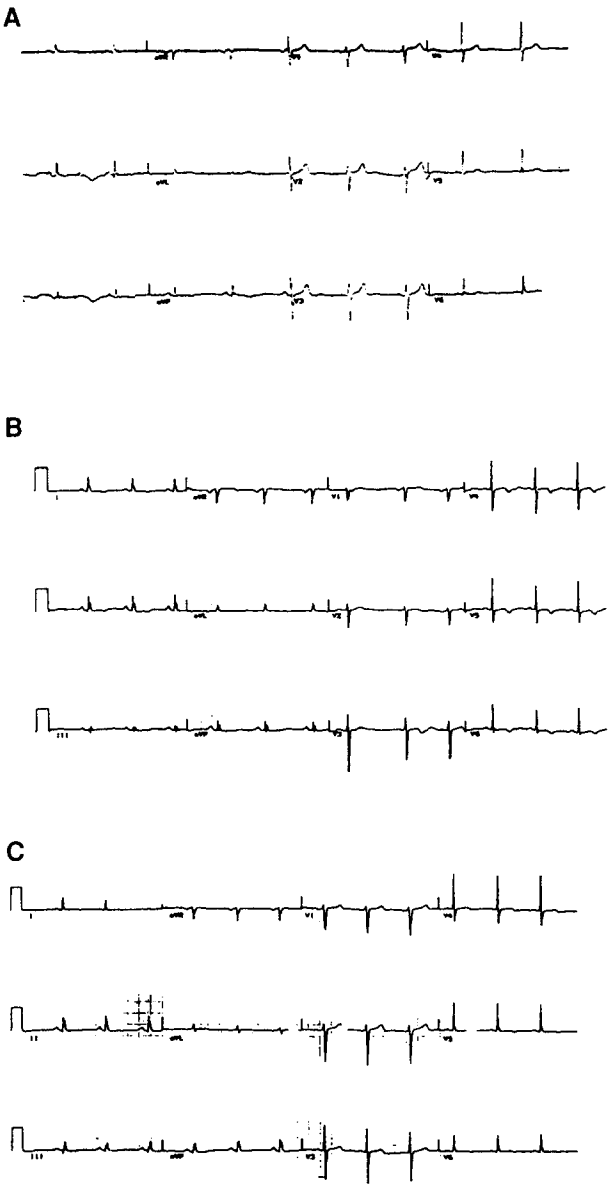


Figure 2. Typical ECG changes seen in patients with left insular lesion. Note the repolarisation changes (T wave inversion). (A) The premorbid ECG obtained four years prior to stroke; (B) the ECG on the day of admission and (C) shows the ECG after two months. Note the partial resolution of the repolarisation abnormalities

ware (Keithley, Rochester, NY, USA). Acquisition and analysis were performed using a Gateway 486 PC computer, incorporated into the acquisition platform. A double buffering system created a buffer of 12 288 samples with 4096 points sampled from each of these three data channels, successive points therefore representing points derived from each of the three monitored signals. All 4096 points of the ECG data were used, whereas the slower waveforms of blood pressure and respiration were read into 512 point arrays. These arrays were used for temporary storage of the data and were used for the on-line analysis. Once this was completed, the raw data was stored in a circular buffer as an ASYST data file. This comprises all 75 such files, representing 10.24 min of acquired data. The circular buffer existed as a virtual disc in RAM.[30]

*ECG R wave peak detection algorithm, artefact rejection and FFT*

To detect the R wave, the ECG signal was differentiated and the result scanned for points exceeding a preset threshold. The threshold was determined automatically during an 8 s initialisation period of acquisition.[30] The first of the series or points exceeding this threshold is considered the onset of the R wave. This methodology assumes that the shape of the R wave will not vary significantly during the observation period. The accuracy of the method was checked against visually determined RR intervals. The algorithm produced RR intervals with an accuracy of 2 ms when compared with the visually determined benchmark. There is a 1 ms uncertainty inherent in the sampling frequency of 500 Hz, so that the overall accuracy of this peak detection algorithm is ± 3 ms or ± 0.3% of the RR interval at 60 beats/min. An RR series is thus obtained which is converted to an evenly sampled instantaneous tachogram necessary for FFT analysis using an algorithm derived by Berger and colleagues.[33]

The FFT was compiled using 1024 data points (4.267 min of data). Sequential intervals were analyzed over the one hour of observation. The Blackman–Tukey algorithm was applied which computes the power spectrum as the Fourier transform of the windowed autocorrelation estimate of the input time series.[34] Prior to obtaining the Blackman–Tukey data, a cubic least-squares curve is applied to the RR interval data to calculate the DC and very low frequency component of the signal, thus detrending the signal. This DC component is removed from the array. This is necessary to remove baseline shifts which produce a peak which would contaminate (lead into) the areas of interest. This was applied to the heart rate data which was first evenly sampled in time, thus avoiding the problems due to inherent biases in beat-indexed signals.[33] This process is equivalent to taking the reciprocal of the RR series and convolving it with a 'boxcar' window which is twice as wide as the desired sample interval of the resulting tachogram signal. Since the human heart rate is modulated at frequencies of 2 Hz or less,[33] we chose a sample rate of 4 Hz for our derived tachogram signal. A Gaussian window was used to smooth the spectrum effecting a frequency resolution of the order of 0.01 Hz.

Ectopic beats and movement artefacts are removed as follows: if two successive heart rate values differ by more than a preset value, the first value is marked as the last valid data point preceding a noise segment. The preset values were determined empirically and were six beats/min/sample over seven points. The following data points are marked as noise until the heart rate signal has stabilised near the last valid heart rate value or at some new rate. A linear spline over each segment is computed and the noisy values replaced with the linearly splined data.[35]

We investigated the power distributed within two designated bandwidths: the LF component (0.04–0.15 Hz) and the HF component (0.15–0.40 Hz). As already mentioned, these correspond to the mixed component of non-respiratory sympathetic and parasympathetic tone and the respiratory parasympathetic oscillatory component, respectively.[17] These data are normalised to the total power as these components are largely age-independent.[32]

*ISE (instability of spectral energy)*

Over the 60 min or so of observation, we obtained 14 sequential power spectral analyses for both patients with insular lesions and the control group. This allowed estimation of the variability in the distribution of spectral energy within the designated HF and LF bandwidths. This variance, termed the instability of spectral energy (ISE), was defined as the variance of the peak ratio (for example Hi/total) divided by the mean of the peak ratio over the entire timing of observation. It is suggested that this function estimates variability in the cardiovascular oscillators controlling heart rate and blood pressure with time.

*Phase and coherence analysis*

The same methods as outlined above were used to obtain the power spectrum of the blood pressure and the complex transfer function calculated as below for an input signal $x(t)$ and an output signal $y(t)$:

$$H(q) = \frac{Sxx(q)}{Sxy(q)}$$

where $Sxx(q)$ is the autospectrum of the input and $S(xy)q$ is the cross-spectrum of the input and the output. The phase component of $H(q)$, $(q)$ is given by:

$$(q)\tan^{-1} = \frac{H_I(q)}{H_R(q)}$$

where $H_I(q)$ denotes the imaginary part and $H_R(q)$ the real part of $H(q)$. Using HR as the input signal and blood pressure as the output signal the phase relationships between these signals can be evaluated. Phase and coherence were evaluated for the HF and LF bandwidths. Coherence was considered to exist only if this value was greater than 0.5 within these bandwidths.[36] At frequencies where coherence was established, the phase relationship between heart rate and blood pressure was determined. A coherence-weighted average transfer function representing the one hour session was calculated, producing a phase angle relationship in which emphasis was only placed on the coherent frequencies of the signals.

*Complexity analysis*

In addition to the above deterministic measures of heart rate variability, other methods can be applied to analyze complex waveforms and estimate apparent randomness or unpredictability. Chaos applications are such measures but still imply determinism within the system. One derivative of chaos theory, the correlation dimension, was accordingly used to estimate if differences in complexity exist between our lesion and control groups. In addition, we have applied two new methods derived from mathematical statistics (approximate entropy and $\psi^2$, defined below), which do not assume the presence of a deterministic process. To our knowledge, $\psi^2$ has not been applied previously to biological data.

*The correlation dimension.* The correlation dimension is a measure of the degree of apparent randomness present within a system. However, this methodology cannot be used to establish whether systems are random or chaotic as certain types of random systems may yield non-integer values (taken as an indication of the presence of chaos). We suggest that if the left insular cortex were involved in cardiac control, lesions of this region should decrease the correlation dimension. The correlation dimension of the first difference of the RR time series was calculated using an algorithm devised by Dr Mark Shelhammer (John Hopkins University). This involves reconstructing the phase space attractor in successively higher 'embedding dimensions' until the estimated dimension becomes invariant. Thus, having reconstructed the attractor in a multi-dimensional Euclidian space containing $M$ independent axes, each attractor of embedding $M$ has its correlation dimension calculated using the method of Grassberger and Procaccia.[37] The correlation integrals $C(r)$ are calculated and a scaling region evaluated in which the correlation integral scales as $r^d$. The value of $d$ is the correlation dimension for the attractor at the given embedding dimension. Successive embeddings are made, until $d$ becomes independent of $M$, which is the final correlation dimension of the system. If such saturation occurs, then the system may have deterministic characteristics (including chaos), whereas if $d$ increased continuously, the system is entirely random.

*Approximate entropy.* Complexity can also be assessed using approximate entropy, a measure of randomness which makes no assumptions about the behaviour or descriptors of the system.[26] In general, the method explores the likelihood that segments of a time series that are similar will remain so when the segments of that time series increase in length. As with the correlation dimension, the methodology involves time series embedding and the correlation integral as follows: a time series $\{u(i)\}$ of length $N$ is embedded in two successive dimensions $m$ and $(m + 1)$, and the correlation integrals associated with each embedding are calculated. If these differ, then randomness is likely since the method in essence measures the degree of similarity between the calculated vectors comprising each time series and a template vector.[26]

*The $\psi^2$ statistic.* This method measures the distance of a signal from that of a given reference signal, which, in the case of these investigations was white Gaussian noise.[27] The more regular and removed from Gaussian noise a signal becomes, the larger is its $\psi^2$ value. The statistic is obtained by a higher order crossing sequence (HOC) in which filterings are used which are successive orders of the difference operator.

$$\nabla Z_t = Z_t - Z_{t-1}$$

Given a zero-mean discrete time series $\{Z_t\}$ the simple higher order crossings series $\{D_k\}$ is defined as

$$D_1, D_2, D_3, \ldots\ldots D_k$$

where $D_1$ is the number of zero-crossings in $\nabla\{Z_t\}$, $D_2$ is the number of zero-crossings in $\{Z_t\}$, $D_3$ is the number of zero-crossings in $\nabla^2\{Z_t\}$ and so on. In general, $D_n$ is the number of zero crossings in $\nabla^{n-1}\{Z_t\}$. Each element $D_n$ is always evaluated from differenced records of the same length $N$.

Simple higher order crossings series tend to increase monotonically with high probability, and their initial rate of increase serves as a powerful discriminator. The $\psi^2$ statistic quantifies this initial rate of increases and is defined as:

$$\psi^2 = \sum^k k = 1(\Delta k^{-m} k)^2 / m_k$$

where $\Delta k$ is the increment between successive zero-crossing counts

$$\Delta k = D_1, \text{ if } k = 1$$
$$D_k - D_{k-1}, \text{ if } k = 2, \ldots . k-1$$
$$(N-1) - D_{k-1}, \text{ if } k = K$$

and $Mk = E[\Delta_k]$ ($E$ is the expected value). In order to reference this against white noise the $Mk$ values corresponding to white Gaussian noise are used which have been derived analytically.[27]

*Statistical analysis.* The distribution of variables was assessed and where Gaussian, parametric measures were applied (unpaired $t$ test). When non-parametric distributions were demonstrated, the Mann–Whitney $U$ test was employed. Statistical significance was set at $p < 0.05$.

This investigation was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Hospital.

## Results

Mean arterial blood pressure significantly increased with age ($p < 0.05$). However, there was no statistically significant change in heart rate with age. Interestingly, whereas total power of heart rate variability decreased with age ($p < 0.005$) normalised Hi/total and Lo/total power showed no such age-dependency consistent with the results of others.[32] Consequently, for age-dependent variables an age-matched group selected from the total control group was chosen, whereas where there was no age dependence the entire control group ($n = 17$) was used.

*Time-domain characteristics*

There was no difference in the mean arterial pressure between the left insular lesion group (mean age and SD from above) and an age-matched group of seven patients (53 ± 6.6 years) selected from the control group over one hour of observation (Table 1). There was a trend towards an increase in heart rate in the patients with left insular lesions which just escaped significance ($p < 0.06$). Respiration rate was likewise not significantly different between the groups.

*Frequency domain characteristics*

There was a trend towards an increase in total power in the patients with left insular lesions which was not significant when compared to an age-matched group. Likewise a trend was seen towards a decrease to Hi/total power (indicative of parasympathetic tone) and an increase in Lo/total power (suggestive of sympathetic tone) in patients with left insular lesions (Table 2). That these results are indicative of a shift towards increased sympathetic tone, and decreased parasympathetic tone in patients with left insular lesions is suggested to Figure 3. This shows that the frequency domain characteristics of patients with left insular lesions are similar to the control population on standing. This manoeuvre produced statistically signifi-

Table 1. Cardiovascular and respiration data

| | Left insular lesion | Control group | Probability |
|---|---|---|---|
| Mean heart rate | 77± 6 | 64 ± 2 | 0.06 |
| Mean arterial pressure* | 91 ± 12 | 97 ± 3 | NS |
| Mean respiratory rate | 20 ± 1 | 17± 2 | NS |

Cardiovascular and respiration data from patients with left insular lesions ($n = 7$) and a control group ($n = 17$). Figures represent the mean ± standard deviation. *Age dependent variable; statistical significance was assessed using an age-matched control group ($n = 7$; mean age: 53 ± 7 years).

Table 2. Frequency domain spectral data

| | Left insular lesion | Control group | Probability |
|---|---|---|---|
| HR Hi/total | 0.26± 0.06 | 0.37 ± 0.03 | NS |
| HR Lo/total | 0.73 ± 0.06 | 0.62 ± 0.03 | NS |
| HR Hi/Lo | 0.44 ± 0.14 | 0.71 ± 0,09 | NS |
| ISE Hi/total | 0.01 ± 0.03 | 0.02 ± 0.003 | 0.02 |
| ISE Lo/total | 0.006 ± 0.003 | 0.015 ± 0.003 | 0.02 |
| ISE Hi/Lo | 0.05 ± 0.02 | 0.15 ± 0.03 | 0.02 |
| ISE total | 9.1 ± 4 | 20.1 ± 6 | NS |

Frequency domain spectral data showing significant values for the instability of spectral energy (ISE) between the control group ($n = 17$) and those with left insular cortex lesions ($n = 7$). None of these variables showed age-dependency. Hi, High frequency component of power spectral analysis of heart rate (HR); Lo, low frequency component. Statistical analysis employed the Mann–Whitney $U$ test.

cant increases in Lo/total power ($p < 0.02$), decreases in Hi/total power, ($p < 0.02$), together with a significant fall in blood pressure ($p < 0.03$) and a significant increase in heart rate ($p < 0.0001$) in the group of 17 control individuals. Significant changes also were observed in ISE; there was a significant reduction in both Hi/total and Lo/total ISE in patients with left insular lesions ($p < 0.02$) (Table 2). However, there was no difference in the ISE of total power between the two groups. This suggests that insular lesions decrease the normal fluctuations seen over time in the oscillators controlling heart rate variability, and suggest a shift towards a greater degree of determinism and away from randomness in these patients.

*Phase and coherence data*

The number of individuals expressing coherence within the Hi and Lo frequency bandwidths was investigated (Table 3). No significant association with age was seen in the control population. Coherence was only observed between blood pressure and heart rate signals in approximately 50% of patients. In controls, where coherence was established the mean phase angle between blood pressure and heart rate was of the order of −100° (blood pressure leading heart rate)

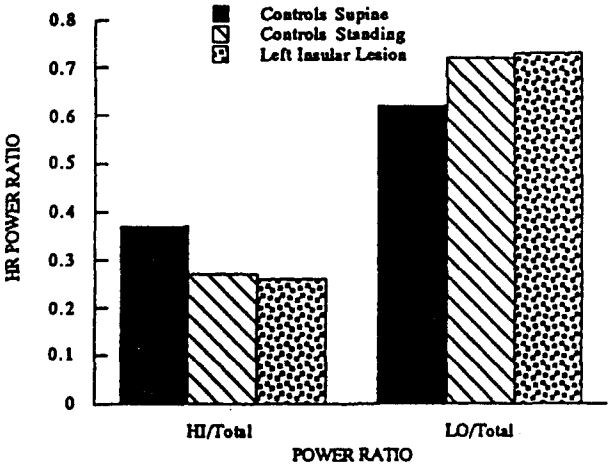


Figure 3. The increase in Lo/total power and the decrease in Hi/total power seen in patients with left insular lesions (stippled bars), mimics the changes seen in the controls on standing for 10 min (hatched bars) from a supine position (filled bars). This suggests that left insular lesions are associated with an increase in sympathetic tone and a decrease in parasympathetic tone

Table 3. Coherence and phase angle (in degrees) data for supine control group according to age

| | Hi | Lo | Probability |
|---|---|---|---|
| No. showing coherence Age < 50 ($n = 10$) | 4/10 | 5/10 | NS |
| No showing coherence Age > 50 ($n = 7$) | 5/7 | 3/7 | NS |
| Mean phase angle Age < 50 | −141 ± 28 | −96 ± 9 | NS |
| Mean phase angle Age > 50 | −92 ± 21 | −123 ± 35 | NS |

The phase angles were determined for those individuals showing coherence > 0.5 within the Hi and Lo frequency bands.

Table 4. Comparison of number of individuals showing coherence and their phase angle relationships

| | Controls Hi | Controls Lo | L insular Hi | L insular Lo |
|---|---|---|---|---|
| No. showing coherence > 0.5 | 4/7 | 3/7 | 1/6 | 4/6 |
| Mean phase angle (degrees) | −114 ± 18 | 106 ± 13 | 0 | 10 ± 39* |

These figures are obtained from an age-matched control group over 50 years of age (Control). The comparison is with a matched group of six patients with acute left insular stroke over 50 years of age (L insular). Demographic characteristics are given in the text. *$p < 0.03$ (Mann–Whitney $U$ test) for comparison with Lo frequency band in control group.

Table 5. Complexity measures

| | Left insular lesion group | Control group |
|---|---|---|
| Correlation dimension | 6.2 ± 0.3* | 7.5 ± 0.5 |
| Approximate entropy | 1.0 ± 0.2 | 1.3 ± 0.09 |
| $\psi^2$ | 2077 ± 338 | 1288 ± 219 |

*$p < 0.04$ (Mann–Whitney $U$ test).
Complexity measures for left insular lesion and control groups (these are age-matched for approximate entropy and correlation dimension which are age dependent variables).

(Table 4), showing no significant difference with age or frequency bandwidth. In patients with left insular lesions there was a significant difference compared with controls in the phase angle for both frequency bandwidths (Table 4). Thus, the normal lag whereby arterial pressure lags behind heart rate was abolished in patients with left insular lesions.

*Complexity analysis*

The correlation dimension of the control group was significantly greater than that of patients with left insular lesions (Table 5). However, calculation of this measure was problematic in part because the correlation integrals did not exhibit well-defined scaling regions.

Approximate entropy was reduced in patients with left insular lesions, although this failed to reach significance (Table 5). This suggests a decrease in the complexity of heart rate variability in patients with such lesions. Similar findings were seen with respect to $\psi^2$ which was increased in patients with left insular lesions although this did not reach statistical significance (Table 5). Increases in $\psi^2$ imply increased randomness.

## Discussion

*The insular cortex and cardiac autonomic tone*

We specifically investigated the effect of left insular lesions on cardiac autonomic tone and complexity. These studies follow logically from our previous laboratory work and investigations in humans. A site of representation of cardiac autonomic regulation was

identified within the rat insula[9] with bradycardia sites situated caudal to those from which tachycardia could be induced. In humans undergoing surgery for control of intractable epilepsy, stimulation of the anterior right insular cortex resulted in tachycardia associated with increases in blood pressure.[13] Left insular stimulation most frequently resulted in bradycardia and decreases in blood pressure. It is suggested therefore that lesions confined in the main to the left insular cortex, by destroying a cortical area of cardiac parasympathetic representation, could shift basal cardiac autonomic tone towards enhanced sympathetic drive. Such enhancement may well have a pro-arrhythmic effect and contribute to the increased cardiac mortality seen after stroke. Thus, in the time domain, we demonstrated that patients with left insular lesions showed an increase in heart rate compared to age matched controls which just escaped significance ($p < 0.06$).

It has been suggested that cardiovascular autonomic tone is determined by a sequence of partially coupled non-linear oscillators distributed throughout the neuraxis.[38] It is conceivable that the frequency components dissected from the heart rate power spectra correspond to characteristics related to some of these controlling oscillator networks. Thus, the high frequency (parasympathetic) component may reflect the activity of controlling oscillators mainly associated with respiratory activity. The low frequency components most probably reflect the activity of oscillatory networks distributed throughout the neuraxis concerned with cardiac sympathetic control. There was a trend towards frequency domain measures of increased cardiac sympathetic tone and decreased parasympathetic tone over the one hour of observation. That these effects were not secondary to baroreceptor activation or respiratory changes is shown by the absence of differences in mean arterial pressure or respiration between the groups. While trends appropriate to the hypothesis were observed, statistical significance was not attained in many of the simple power spectral derivatives of cardiac autonomic tone. Several possibilities may account for this: although the lesions mainly involved the insular cortex, in most cases there was some involvement of adjacent frontoparietal cortex. Owing to the anatomical arrangement and vascular supply of the insula, lesions involving this region are rare, and those entirely confined to the insula are not encountered. Our patients were selected on the basis that these lesions were sited on the insula and peri-insular involvement defined by the MRI scan was minimised. However, it is possible that the effect of this extra-insular involvement may dilute the effects which would otherwise have been seen had the lesions been solely localised to the insula. Secondly, because we are dealing with the highest level of cardiac representation (the cortex) many synapses removed from the heart, the overall effects in the basal state may be subtle. When more subtle measures of oscillator function were investigated (ISE), significant differences were seen. Left insular lesions markedly reduced high and low frequency peak variability over the 60–80 min period of observation. This suggests a reduction in the inherent secular variability of the neuraxial oscillators controlling cardiac autonomic tone induced by these insular lesions.

Recently, Barron and colleagues investigated the effects of hemisphere stroke on cardiac autonomic tone using fast Fourier analysis.[39] Total spectral power was reduced irrespective of laterality when compared with an age-matched group. Likewise, hemisphere stroke was associated with a reduction in parasympathetic tone, with a significantly greater effect seen for right-sided lesions. It is to be noted that whereas the lesions were located within the middle cerebral artery territory as in our study, the authors did not comment on the extent of insular involvement (if any).

In another study, Sander and Klinghoeffer showed that insular lesions abolished the nocturnal decrease in blood pressure usually seen on continuous blood pressure monitoring.[40] It was suggested that this represented an increase in basal sympathetic cardiovascular tone. In keeping with this, an increased basal norepinephrine level (but not epinephrine) was observed, suggesting an extra-adrenal, probably neuronal source of the increased sympathetic activity. Moreover, patients with insular lesions demonstrated a significant prolongation of their QT interval compared with matched patients with stroke in other locations. These findings also correlated with a 55% incidence of ventricular tachyarrhythmias and high grade heart block. This study did not investigate the effects of stroke lateralisation.

Vingerhoets and colleagues have recently demonstrated that left parieto-insular strokes are more frequently associated with the onset of acute atrial fibrillation than are lesions in other locations.[41] It was argued that the arrhythmia was a post-infarction onset on the grounds that no evidence of antecedent arrhythmia had been demonstrated, there was no acute cardiac or pulmonary cause for the lesion, and the arrhythmia developed following the patients' admission and then vanished, with recurrence during follow up. These observations strongly suggested that the arrhythmia was associated with the stroke, rather than serving as a cardio-embolic cause for its occurrence.

In a rat stroke model, we demonstrated that experimental occlusion of the right middle cerebral artery increased QT interval and plasma norepinephrine significantly over similar left arterial occlusion. In all cases the insular cortex was included in the lesion.[42] However, the strokes caused by this model were large including adjacent peri-insular regions. This may account for the differences in laterality seen in this and in human studies quoted earlier. Alternatively, there may be a species disparity in the laterality of cardiovascular autonomic representation.

Our patients were not hypertensive and had no additional diseases which could have affected their status.

They were not receiving cardio-active medications. It is therefore unlikely that these observations represented the effects of these adventitious circumstances.

*Coherence and phase relationships*

In keeping with the ISE findings, the alterations in cardiovascular phase relationships induced by left insular lesions strongly suggest that the lesions alter the interactions between the neuraxial oscillatory mechanisms controlling cardiovascular tone. In our control group, we did not show an age dependency in either the number of patients demonstrating coherence or in the phase angle of the relationship. Not all patients demonstrated coherence in the designated spectral peak bandwidths using our criteria of coherence of 0.5. This proportion did not differ significantly from our insular lesion group.

Others have shown that coherence exists between the high and low signal components of blood pressure and heart rate spectral power.[43] In general, heart rate lags blood pressure at the lower frequency bandwidth and leads it at higher frequency. Our data however, demonstrated that mean arterial blood pressure lagged heart rate at both high and low frequency bandwidths in our control group. These discrepancies are possibly explained by differences in methodology. Evenly sampled heart rate and blood pressure signals were used in this study, whereas Pagani and colleagues used RR interval and beat to beat blood pressure data. These beat indexed signals can induce artefacts into spectral estimations which could affect the phase measurements of these signals.

A higher percentage of patients with left insular cortex lesions demonstrated coherence at the lower than at higher frequency bandwidths. This may reflect the increase in lower frequency spectral energy and the decrease in higher frequency spectral energy seen in these patients. The higher the spectral power, the greater the likelihood of the demonstration of coherence. At low frequency, a significant change in phase angle was seen in patients with left insular lesions. This approached 0° in these patients. There are two explanations for this: either the HR and mean arterial pressure signals could be entirely in phase or, there is a random distribution such that the overall mean value is close to 0°. This latter was the case. This suggests that while the heart rate and mean arterial pressure signals are both varying with similar frequencies (hence the coherence) the phase angle between the two signals varies, which implies decoupling. Only one patient with a left insular lesion demonstrated coherence at high frequency and the phase angle was 0° in this case. This again is in keeping with a decoupling of the oscillatory interactions controlling heart rate.

*Heart rate complexity*

In general, our data are consistent with a reduction in the overall level of complexity in heart rate variability induced by left insular lesions. The correlation dimension was significantly decreased in the patient group. All other measures showed trends which are consistent with this tendency but failed to reach statistical significance in this small sample of patients. When properly functioning, the left insular cortex may well act to increase heart rate complexity in keeping with its suggested role in control of parasympathetic function.

Our values for the correlation dimension in the normal group agree with those of others.[18,23] However, the suitability of this application is controversial. Whereas our data demonstrated a scaling region this did not fully conform to rigid criteria as a discontinuity over a full decade was not demonstrated either in the control or lesion group. Truly chaotic attractors do exhibit proper scaling, however HRV appears not to be a low-dimensional chaotic process.[23,24] Our data would be in agreement with this observation.

*Study limitations*

We chose to study patients with left insular lesions, without concomitant cardiovascular disease or complicating factors. Such patients are exceptionally rare and account for the small numbers in this study. As a result, some of our data, while showing a trend in the direction of the hypothesis, did not reach statistical significance. A prolonged investigation extending over many years with recruitment of larger sample size may resolve this issue. Likewise, we did not identify patients with acute right insular lesions during the recruitment phase of the study so that it is unclear whether such patients might show similar changes or whether a tendency towards increased heart rate variability, as predicted by the hypothesis, might be seen.

It should be stated that we believe this study to be indicative rather than definitive. As comparisons have not been conducted in patients with strokes in other locations, we are unable to answer the question as to whether insular location is important in determining the changes reported, as opposed to just stroke per se, independent of location. However, these results could be anticipated from earlier animal experimentation and human observation (see Introduction).

The prognostic significance of the changes which we have identified is unclear at this stage and is the subject of a current study.

Power spectral analysis affords only an indirect measure of cardiac autonomic tone. Whereas the major peaks have been identified with the principal limbs of the autonomic nervous system, this is by no means pure and there is probably state and disease variability. Direct neural recordings from cardiac nerves are however impossible in the human, and measurements of plasma catecholamine levels are even more indirect, as they really only reflect spill over from synapses and adrenal tone. At the moment, as poor as it is, spectral analysis represents the best indirect measure which we have of cardiac autonomic tone.

*Implications of the study*

Cardiac events constitute the single commonest cause of mortality and morbidity after stroke. We suggest that derangements resulting in damage to the left insular cortex, or stroke-related trauma in the right peri-insular region [which may have an inhibitory effect on sympathoadrenal function (SM Oppenheimer, unpublished observations)] may shift autonomic balance towards increased cardiac sympathetic tone and decreased parasympathetic tone. A reduction in complexity as manifested by a decrease in ISE and a tendency towards a decrease in approximate entropy or an increase in $\psi^2$ also occurs in such patients. It is conceivable that these shifts in aggregate predispose patients towards a pro-arrhythmic state. In addition, our data suggest an important involvement of the insular cortex in the oscillatory relationships controlling heart rate and blood pressure. Thus the phase angle disturbance generated by left insular lesions could indicate decoupling of oscillators at lower neuraxial levels, for example in the brainstem. As a consequence, we suggest that patients with left insular lesions may be a subgroup who require careful cardiovascular monitoring after stroke.

We also believe that the demonstration of the involvement of the insular cortex (a site of limbic autonomic convergence) in heart rate control may identify a physiological mechanism whereby perception of emotional stress could derange cardiac autonomic tone. This might be of particular importance when there is coronary ischemia or structural cardiac damage. The anecdotal reports of voodoo death, or death from a broken heart may indeed have an explicable physiological basis.

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