RESEARCH PAPER

Complexity of heart rate variability predicts outcome in intensive care unit admitted patients with acute stroke

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ABSTRACT

Background Heart rate variability (HRV) has been proposed as a predictor of acute stroke outcome. This study aimed to evaluate the predictive value of a novel non-linear method for analysis of HRV, multiscale entropy (MSE) and outcome of patients with acute stroke who had been admitted to the intensive care unit (ICU).

Methods The MSE of HRV was analysed from 1 h continuous ECG signals in ICU-admitted patients with acute stroke and controls. The complexity index was defined as the area under the MSE curve (scale 1–20). A favourable outcome was defined as modified Rankin scale 0–2 at 3 months after stroke.

Results The trends of MSE curves in patients with atrial fibrillation (AF) (n=77) were apparently different from those in patients with non-AF stroke (n=150) and controls (n=60). In addition, the values of complexity index were significantly lower in the patients with non-AF stroke than in the controls (25.8±3 vs 32.3±4.3, p<0.001). After adjustment for clinical variables, patients without AF who had a favourable outcome were significantly related to higher complexity index values (OR=1.15, 95% CI 1.07 to 1.25, p<0.001). Importantly, the area under the receiver operating characteristic curve for predicting a favourable outcome of patients with non-AF stroke from clinical parameters was 0.858 (95% CI 0.797 to 0.919) and significantly improved to 0.903 (95% CI 0.853 to 0.954) after adding on the parameter of complexity index values (p=0.020).

Conclusions In ICU-admitted patients with acute stroke, early assessment of the complexity of HRV by MSE can help in predicting outcomes in patients without AF.

Acute stroke commonly affects the autonomic nervous system and induces cardiovascular responses.1–3 Heart rate variability (HRV) has been proposed as a measurable parameter that could represent autonomic activities.4–8 Studies have shown that a reduction of HRV is a general index of illness, including in patients with stroke.9–15 However, most of the previous studies applied conventional linear models to analyse the HRV, even though modulation of the autonomic nervous system on cardiovascular signals is thought to be non-linear physiologically.16–18

Recently, the multiscale entropy (MSE) has been used to quantify the complex regulatory dynamics of human biological signals, such as HRV.19–21 MSE non-linearly quantifies time series at different temporal scales using an entropy-based algorithm and profiles the embedded ‘complexity’ structure based on a heartbeat fluctuation. The quantifiable character of MSE analysis of HRV has been applied to demonstrate the effect of carotid stenting on the alternation of autonomic activities and as an outcome predictor for patients with traumatic head injury.19–20 However, MSE analysis of HRV after acute stroke and its association with post-stroke outcome have not been studied previously.

This study aimed to investigate the complexity of HRV via MSE analysis as well as its association with 3-month functional outcome in patients with acute stroke admitted to the intensive care unit (ICU) as compared to non-stroke controls.

PATIENTS AND METHODS

Study design

This prospective case–control study was conducted at the stroke ICU of the National Taiwan University Hospital (NTUH), with the approval of the Research Ethics Committee of NTUH. Written informed consent was obtained from the patient or the next of kin of patients with decreased consciousness.

Patients

Patients with acute stroke who had been admitted within 24 h to the stroke ICU during February 2012 and August 2013 were prospectively recruited. Age-matched and sex-matched control participants with regular sinus rhythm and free of any acute cardiovascular events within 12 months were recruited from inpatients for health check-up.

The entry criteria of our stroke ICU included patients with ischaemic stroke receiving thrombolytic therapy or endovascular treatment, patients with intracerebral haemorrhage receiving aggressive blood pressure (BP) control, severe neurological deficits (eg, National Institute Health Stroke Scale (NIHSS) score higher than 8), stroke in evolution or medical conditions requiring intensive care. We excluded patients who had subarachnoid haemorrhage because their prognostic factors may have been different from those for ischaemic stroke and intracerebral haemorrhage. Other exclusion criteria included modified Rankin scale (mRS)>2 prior to the stroke, symptomatic cardiac failure, inability to
obtain ECG signals within 48 h after admission, and poor quality (artefacts) of ECG signals.

The diagnosis of acute stroke was confirmed by the head magnetic resonance image or repeated CT examination 24 h after stroke onset. Stroke locations were classified as supratentorial or infratentorial regions. All patients received standard intensive care and monitoring of vital signs (BP, ECG, respiratory rate and oxygen saturation).

Demographic background data were documented. Laboratory results at admission, including a complete blood count, biochemistry and glucose, were recorded. BP-lowering medications during the period of ECG recording were classified as β-blocker, calcium channel blocker, ACE inhibitors, angiotensin receptor blockers and others (e.g., diuretics and α-blocker). Uses of diabetic medication, lipid lowering agent and antiplatelet agent were also recorded. Stroke severity was identified as the admission NIHSS score. For patients with ischaemic stroke who received thrombolytic therapy, NIHSS score at 24 h after thrombolytic therapy was used for further analysis. Favourable outcome was defined as mRS 0–2 at 3 months after stroke onset.

Blood pressure and heart rate monitoring
After admission, data of brachial systolic and diastolic BP and heart rate (HR) were regularly measured every hour. We characterised BP and HR data in the first 24 h of admission by calculating the following values: mean and SD of systolic BE diastolic BP and HR.

ECG data acquisition
We set up a standard procedure for collecting ECG analogue data directly from the stroke ICU bedside monitor (Philips Intellivue MP70). 1 h ECG data were digitised with a sampling rate of 512 Hz and stored in the computer. Respiratory care, physiotherapy and physical manipulations were avoided during this recording period. For control participants, ECG signalling was obtained using a Holter monitor (MyECG E3-80, Mircostar Company, Taipei, Taiwan). The stored ECG data were screened for body movement, muscle and other artefacts. Before analysis, these data went through a pre-processing step to extract the R wave to R wave interval (R–R interval) time series. Atrial fibrillation (AF) rhythm was indicated as the absence of P waves with disorganised electrical activity in their place and irregular R–R intervals.

Linear analysis
The measurements of HRV were calculated from 1 h ECG data using previously described methods.\(^1\)\(^2\)\(^3\)\(^4\) We computed two time domain measures: SD of normal to normal R wave, reflecting the overall variability magnitude and the root-mean-square of successive beat-to-beat differences (RMSSD), reflecting the average magnitude of change between two successive beats. The frequency domain analysis of HRV was carried out by fast Fourier transform. The following measures were derived: high-frequency power (0.15–0.4 Hz), low-frequency power (0.04–0.15 Hz) and the ratio of low-frequency to high-frequency power.

Non-linear analysis
The MSE analysis was applied on 1 h ECG data using methods described previously.\(^6\)\(^7\) It is a non-linear method measuring the complexity of a time series. Briefly, the MSE method comprises two main steps: (1) coarse-graining the signals into different time scales and (2) sample entropy calculations for each coarse-grained time series. For a given time series \(\{x_i\}_{1 \leq i \leq N}\), the coarse-grained time series \(y_j^\tau\) is calculated according to the equation

\[
y_j^\tau = \frac{1}{\tau} \sum_{i=0}^{N-\tau} x_{i+j},
\]

where \(\tau\) is the scale factor and \(1 \leq j \leq N/\tau\). In this study, we coarse-grained the original time series up to a scale factor of 20, which is a typical choice in most studies. Importantly, although MSE was successfully applied in physiological signals, the entropy values evaluation can be vulnerable to trends. The entropy values can be underestimated when a trend or a background signal exists. Therefore, a de-trending process was performed prior to calculation of multiscale entropy. In our study, the ensemble empirical mode decomposition method was used to remove the trend of the R–R interval time series. A single value named the complexity index was obtained as the area under the MSE curve (1–20 scales).

Statistical analysis
The clinical characteristics according to controls, patients with AF stroke and patients with non-AF stroke, and functional outcomes were compared using Fisher’s exact test, \(\chi^2\) test, Student \(t\) test, and Mann-Whitney U test with relevant variables as indicated. Figures of the MSE curves and complexity index values were presented as the mean±SEM. The multivariable logistic regression analysis models were used with a favourable outcome (mRS≤2) as the dependent variables. The independent variables in the analyses were age, gender, stroke type, NIHSS and glucose level at admission, smoking and diabetes mellitus. The receiver operating characteristics (ROC) curve was created to explore the ability of clinical parameters and complex index values in predicting post-stroke favourable outcome. Estimates of the area under these curves (AUC) were obtained (AUC=0.5 indicates no discrimination and an AUC=1.0 indicates a perfect diagnostic test). Statistical test results were considered significant if \(p \leq 0.05\). Statistical analysis was performed using the SPSS software package V20.0 (SPSS Inc, Chicago, Illinois, USA) and SAS V9.3 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS
Study patient demographics
During the study period, consecutive patients who were admitted in the stroke ICU and fulfilled the study criteria were recruited. A total of 227 patients with acute stroke were finally included in the analysis. ECG signals were obtained within an average of 22.0±14.4 h after admission. The clinical information for the controls (n=60), patients with AF stroke (n=77) and patients with non-AF stroke (n=150) is listed in table 1. Patients with stroke with a non-AF rhythm and controls had similar mean age, gender and percentage of diabetes mellitus and hyperlipidaemia. Compared to patients with AF stroke, patients with non-AF stroke were younger, had a higher percentage of hypertension, a lower mean NIHSS score and a higher rate of functional independence (all \(p \leq 0.05\)).

MSE curves in study subjects
The trends of the MSE curves in patients with AF stroke were apparently different from those in the control and patients with non-AF stroke (figure 1A). The patients with non-AF stroke had significantly lower complexity index values than did the controls (26.0±8.1 vs 32.3±4.3, \(p < 0.001\)). Figure 1B, C demonstrates the MSE curves in different outcomes in patients with non-AF

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and AF strokes. The sample entropies were apparently higher in patients with non-AF stroke with a favourable outcome than in those without. However, in patients with AF stroke, there was no significant difference of sample entropies between each group, even after adjustment of clinical variables. Furthermore, the relationship between the MSE curves and outcome was similar in the subgroup analysis of stroke types (ischaemic stroke or intracerebral haemorrhage) and stroke locations (supratentorial or infratentorium) in patients with non-AF stroke (figure 2A–D).

Factors related to a favourable outcome in patients with non-AF stroke

Table 2 documents the clinical parameters in patients with non-AF stroke. The variables associated with a favourable outcome included younger age, history of smoking and diabetes mellitus, lower initial glucose levels and lower NIHSS score at admission.

Taking into consideration the various parameters of 24 h BP or HR on the first day of admission and linear analysis of HRV, only 24 h SD of systolic BP showed borderline associations with outcome (p=0.058 and 0.046, respectively). However, higher complexity index values were significantly correlated with a favourable outcome (OR=1.15, 95% CI 1.07 to 1.25, p<0.001) after adjustment of clinical parameters (table 3).

In addition, the effects were similar in subgroup analysis of patients with ischaemic stroke and intracerebral haemorrhage (table 4).

Furthermore, the AUC for predicting a favourable outcome of patients with non-AF stroke for clinical parameters (age, NIHSS score and glucose level at admission and history of diabetes mellitus and smoking) was 0.858 (95% CI 0.797 to 0.919), and for complexity index values it was 0.759 (95% CI 0.678 to 0.834). Importantly, their combination significantly improved the AUC to 0.903 (95% CI 0.853 to 0.954; p=0.020; figure 3).

DISCUSSION

Despite a significant reduction of stroke mortality in the past two decades owing to improvements in acute stroke care, 30–50% of patients with stroke continue to have an unfavourable functional recovery, especially those patients who require treatment and close monitoring in the ICU.22 23 Previous studies have identified several clinical parameters that may be helpful in predicting stroke outcome, including age, gender, stroke severity, initial glucose level and chronic kidney disease, etc,22 24 25 but most parameters are related to the pre-stroke background information rather than post-stroke brain injury.

Several studies showed that the levels of BP and HR at admission or mean value of 24 h BP and HR on the first day of admission might have reverse or U-shaped relationships with outcome.26–29 However, some other reports suggested that those BP or HR parameters are of little or even contradictive prognostic values.22 30 31 In our case series, only 24 h SD of systolic BP showed a borderline association with a 3-month post-stroke outcome in ICU-admitted patients with acute stroke after adjustment of clinical variables.
Unlike simple cut-off values for BP or HR data that may be affected by many internal or external factors under acute stroke conditions, heart rhythm contains more complex physiological information, mainly reflecting the influences of the autonomic nervous system. However, the results are not consistent within different studies, including ours, and it remains unclear as to which parameters are most related to outcome.

Recently, one study compared several non-linear parameters including approximate, sample and fuzzy entropies and conventional linear parameters of HRV in patients with acute stroke. It concluded that entropy values were more like to reflect early neurological status (eg, NIHSS score) within 7 days after stroke rather than long-term prognosis. However, a higher value of entropy from the single time scale non-linear analytic methods simply means that an increase in the degree of randomness but not necessarily an increase in the complexity (white noise series, eg, has a high entropy but low complexity).

In contrast, the MSE analysis calculates entropy over multiple time scales and enables one to successfully clarify the fact of low complexity inside the white noise series. Decreased complexity of HRV as determined via the MSE assay has been demonstrated in normal ageing patients and patients with congestive heart failure and type I diabetes mellitus. When applied to the intracranial pressure waveform, one recent study demonstrated a significant correlation between the complexity of the intracranial pressure waveform and functional outcome in patients with traumatic head injury.

### Table 2

<table>
<thead>
<tr>
<th>Variables related to functional status 3 months after stroke in patients without AF</th>
<th>Modified Rankin scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MRS≤2 (n=64)</td>
</tr>
<tr>
<td>Age, year</td>
<td>57.4±14.7</td>
</tr>
<tr>
<td>Female</td>
<td>28 (44.2)</td>
</tr>
<tr>
<td>Stroke subtype (ICH)</td>
<td>28 (43.8)</td>
</tr>
<tr>
<td>Location (supratentorium)</td>
<td>43 (67.2)</td>
</tr>
<tr>
<td>Systolic BP at admission</td>
<td>171.7±36.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (20.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53 (82.8)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>29 (45.3)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>31 (48.4)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>127.7±54.2</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>174.2±40.3</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.0±0.7</td>
</tr>
<tr>
<td>NIH stroke scale</td>
<td>7.8±6.1</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>30 (46.9)</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Diabetic medication</td>
<td>8 (4.9)</td>
</tr>
<tr>
<td>Lipid lowering agent</td>
<td>21 (32.8)</td>
</tr>
<tr>
<td>Antplatelet agent</td>
<td>22 (34.3)</td>
</tr>
</tbody>
</table>

Values are number (percentage) or mean±SD. ACEI/ARB, ACE inhibitors/angiotensin receptor blockers; AF, atrial fibrillation; BP, blood pressure; ICH, intracerebral haemorrhage; MRS, modified Rankin scale; NIH, National Institute of Health.

### Figure 2

The distribution of multiscale entropy curves versus functional outcomes was similar in both stroke subtypes (ischaemic stroke (A) and intracerebral haemorrhage (B)) and stroke regions (supratentorium (C) and infratentorium (D)) (modified Rankin scale, mRS).
Our study disclosed several novel findings. First, assessing the complexity of HRV via MSE analysis can clearly discriminate between three groups: patients with non-AF stroke; patients with AF stroke; non-stroke controls. Second, higher values of the complexity index significantly associated with favourable outcome in patients with non-AF stroke and this concept can be admitted to the ICU, and obtaining values of HRV requires only 1 h ECG data, our results indicate the potential of routinely obtaining the complexity index from all patients with acute severe stroke.

Interestingly, analysis of our HRV data showed that the values of the complexity index had modest correlations with values of RMSSD and the ratio of low-frequency to high-frequency power (r=0.348 and 0.333, respectively, both p<0.001), but not other parameters from the linear analysis. These findings indicate some linkages within different mathematical methods in approaching the HRV. However, the independent prognostic role of complicity index values clearly demonstrates the superiority of MSE analysis over the conventional analysis of HRV.

There are some limitations to this study. First, our study was performed at a single hospital; further studies using a multicentre study design or a larger sample size of specific stroke subtype may help us to validate our observations and clarify its clinical application. Second, patients with a history of dysautonomia prior to the occurrence of stroke may interfere with the interpretation of HRV. Further studies with a longitudinal study design covering the pre-stroke or chronic phase of stroke with a standard questionnaire and physical evaluation for autonomic function may be considered. Third, although the MSE curve can help in identifying patients with AF stroke, values of the complexity index cannot provide any outcome information in this group. Further efforts to develop a specific mathematical algorithm in addition to ECG signals to simulate the autonomic activities in patients with AF stroke should be encouraged.

In summary, our study comprehensively investigated the relationship between various haemodynamic factors and outcome in ICU-admitted patients with acute stroke. Our results suggest that assessing the complexity of HRV by MSE can not only help in identifying patients with AF, but may also provide an early indicator for predicting outcomes in ICU-admitted patients with non-AF stroke.
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Contributors All authors have contributed to the article by participating in the conception and design, acquisition of the data (SCT, HIJ, YHL, WJJ and PWH), analysis and interpretation of the data (SCT, YHL, CSH, JSS, YLH and DML), drafting of the article (SCT, HIJ, JSS and JSJ) or its critical revision for important intellectual content (DML, AIW, JSJ and MFC), and approval of the final manuscript (SCT, AIW, JSJ and MFC).

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