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ORIGINAL ARTICLE

Detrended fluctuation analysis of blood pressure in preterm infants with intraventricular hemorrhage

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Abstract Very preterm infants are at high risk of death and serious permanent brain damage, as occurs with intraventricular hemorrhage (IVH). Detrended fluctuation analysis (DFA) that quantifies the fractal correlation properties of physiological signals has been proposed as a potential method for clinical risk assessment. This study examined whether DFA of the arterial blood pressure (ABP) signal could derive markers for the identification of preterm infants who developed IVH. ABP data were recorded from a prospective cohort of 30 critically ill preterm infants in the first 1–3 h of life, 10 of which developed IVH. DFA was performed on the beat-to-beat sequences of mean arterial pressure (MAP), systolic blood pressure (SBP) and pulse interval, with short-term exponent (α_1, for timescale of 4–15 beats) and long-term exponent (α_2, for timescale of 15–50 beats) computed accordingly. The IVH infants were found to have higher short-term scaling exponents of both MAP and SBP ($\alpha_1 = 1.06 \pm 0.18$ and 0.98 ± 0.20) compared to the non-IVH infants ($\alpha_1 = 0.84 \pm 0.25$ and 0.78 ± 0.25, $P = 0.017$ and 0.038, respectively). The results have demonstrated that fractal dynamics embedded in the arterial pressure waveform could provide useful information that facilitates early identification of IVH in preterm infants.

Keywords Detrended fluctuation analysis · Fractal · Blood pressure · Neonatal · Intraventricular hemorrhage

1 Introduction

With advancements in neonatal intensive care, the incidence of intraventricular hemorrhage (IVH) has fallen from 30 % in the 1980s to 6 % [1] in preterm infants with very low birth weight (birth weight ≤1,500 g). Rates of IVH and in particular severe grades of IVH with extension into cerebral tissue (grade V IVH) in the Papille system are still a major concern in those extremely preterm infants (<27 weeks gestation) [13]. Fragile cerebral circulation of preterm infants is affected by fluctuations in the systemic circulation associated with the pathophysiology of preterm birth and the first 6 h of life when complex interactions occur between mechanical ventilation and the circulation. Preterm birth <27 weeks is an abnormal event often precipitated by maternal infection, bleeding or hypertension, factors all predisposing to reduced uterine perfusion and thus placental function. Placental dysfunction is a predisposing factor to the fragile blood vessels in the germinal matrix bleeding in a grade I IVH. If this extends into the ventricular system (grade II IVH) and then blocks the

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needed drainage of ventricular fluid via the third and fourth ventricles (grade III IVH), risks of long-term brain damage rise. Venous occlusion in adjacent areas of the cerebral hemispheres can give rise to infarction and significant injury to major motor tracks leading to cerebral palsy or intellectual impairment [12, 15]. The timing of IVH indicates most hemorrhages develop after birth with such factors as resuscitation and cardiorespiratory management during the first 24 h of life being important in the causal pathway [6, 10, 11, 19, 21]. Thus, the ability to identify preterm infants with IVH at an early stage is of great importance in terms of minimizing mortality and morbidity in the neonatal intensive care setting.

A recent study explored the potential application of detrended fluctuation analysis (DFA) for identifying early subtle alterations of heart rhythm that could be predictive of impending IVH in very low-birth-weight babies [20]. DFA has been regarded as a robust method to quantify the scale-invariant (fractal) correlation property of a time series, especially when the signal class cannot be precisely determined. Specifically, this method characterizes the mono-fractal property. Previous studies have adopted this method to evaluate the fractal dynamics of heart rate in various diseases in adult subjects [16, 22]. The DFA method aims at measuring the intrinsic fractal-like correlation properties or self-affinity of the time series, characterized by increasing magnitude of fluctuations with increasing timescale (or decreasing frequency). The degree of fractal scaling can be depicted by the scaling exponent (α) that quantifies the relationship between fluctuations $F(n)$ and timescale n based on the mathematical function $F(n) = Cn^{\alpha}$, with $\alpha = 1$ corresponding to the classical $1/f$ fractal signal [16, 22]. In a prior study, preterm infants who later developed IVH were found to have significantly higher short-term scaling exponent of heart rate compared with those who did not develop IVH [20]. The differing fractal dynamics of heart rate in these two groups of infants have been attributed to the altered autonomic control of the heart associated with the development of IVH.

Assessment of fractal scaling properties in arterial blood pressure (BP) in adult humans based on DFA has also been reported [2–4]. By performing autonomic blockade tests, it was shown that vagal blockade by atropine could lead to an increase in the short-term scaling exponent of BP, whereas central blockade of both cardiac and vascular sympathetic outflow by clonidine would result in a decrease of the exponent [4]. It was therefore suggested that fractal dynamics of arterial pressure were largely influenced by the autonomic nervous system activity. However, the fractal scaling of arterial BP in preterm infants has not been investigated previously.

In this study, we examined whether there was a difference in fractal scaling exponents derived from DFA of arterial BP between preterm infants with and without IVH. It was hypothesized that the infants who developed IVH might have higher fractal scaling exponents of arterial BP, similar to that seen in heart rate fluctuations [20]. The findings could help to establish the potential value of fractal dynamics embedded in the arterial pressure waveform for early identification of brain hemorrhage in preterm infants.

2 Methods

This was a prospective clinical investigation, carried out in a large tertiary neonatal intensive care unit in Sydney, Australia. The study was approved by the Sydney West Area Health Service Human Research and Ethics and conducted according to the World Medical Association Declaration of Helsinki, and informed parental consent was obtained in all cases. The cohort comprised early low-birth-weight infants with gestational age <30 weeks, without significant congenital anomalies who survived at least 2 h. The exclusion of infants with significant anomalies is standard in neonatal research to reduce confounding from congenital factors strongly associated with mortality or long-term disability such as trisomy 13. A single measurement of data with 10 min continuous artifact-free segment from each baby was used for analysis. Out of the 46 infants enrolled in the study, 30 infants had arterial BP recordings with sufficiently long artifact-free segments suitable for analysis. The remaining 16 infants either did not have BP recordings (9 infants) or had considerable amount of artifact in the BP data (7 infants).

2.1 Measurements

Physiological data were collected from the infants within 1–3 h of birth. Intra-arterial BP was measured via an umbilical or peripheral arterial catheter connected to a transducer, calibrated to atmospheric barometric pressure and zeroed to the midaxillary point. The BP signal was continuously acquired via a bedside patient monitor (Philips Agilent Systems, Philip Healthcare, North Ryde, Australia) and recorded by a data acquisition system (ADInstruments, Sydney, Australia) at a sampling rate of 1 kHz. The LabChart software (ADInstruments, Sydney, Australia) provided automatic beat-to-beat computation of systolic blood pressure (SBP), mean arterial pressure (MAP) and pulse interval from the arterial BP waveform. Cranial ultrasound measurements for the diagnosis of IVH were taken within the first 2 h of life and repeated 12 hourly for the first 2 days of life. The scans and assessments were taken in a systematic method with classification scored by a pediatric radiologist blinded to the clinical

outcome and study according to the Papille classification [13].

2.2 Data analysis

Detrended fluctuation analysis was performed on uninterrupted data recordings of 10 min (obtained within 1–3 h after birth from each infant) without noticeable corruption by artifacts. All signal processing was implemented in Matlab (Natick, MA, USA). Spikes in the beat-to-beat time series due to occurrence of abnormal pulse intervals (e.g., prolonged heart period resulting from a missing beat), which constituted less than 3 % of the total number of beats, were removed and replaced by linear interpolation of the beat values immediately preceding and following the replaced beats.

The DFA method has been developed to analyze the scale-invariant (fractal) correlation property of a time series [16]. In this case, the time series would correspond to the beat-to-beat values of SBP, MAP and pulse interval. Consider a time series Y with a total length of N, that is, a total of N beats. For a heart rate of 150 bpm, a 10 min period would consist of $N = 1{,}500$ beats. In the application of DFA, the time series was first integrated to improve the fractal property. This is achieved by calculating the cumulative sum of the differences between the ith parameter value $Y(i)$ and the mean parameter value $Y_{\text{mean}}(i)$:

$$y(k) = \sum_{i=1}^{k} [Y(i) - Y_{\text{mean}}(i)].$$

Next, the integrated time series $y(k)$ is divided into multiple windows of equal length n. For example, for a total of $N = 1{,}500$ beats and for a window size of $n = 15$ beats, there would be 100 windows. Within each window, a trend line is fitted to the data, with $y_n(k)$ denoting the kth point on the trend line with a length of n. The root-mean-square (RMS) fluctuation $F(n)$ of the detrended integrated time series for a given window size n is calculated by

$$F(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N} [y(k) - y_n(k)]^2}.$$

This procedure is repeated at different window sizes to derive the relationship between $F(n)$ and n. Finally, $F(n)$ is plotted against the window length n in a log–log plot, and the slope of the relationship will correspond to the fractal scaling exponent α. For fractal signals, the fluctuations can be expressed as a power-law function of the timescale: $F(n) = Cn^{\alpha}$, in which case $\log_{10}(F(n))$ and $\log_{10}(n)$ are directly proportional with α as the slope of the relationship. The existence of a linear relationship (assessed by the goodness of fit of the regression) between $\log_{10}(F(n))$ and $\log_{10}(n)$ will be considered necessary for the slope α to be a valid measure of fractal scaling. The special case of $\alpha = 1$ is often termed $1/f$ noise, with the power of fluctuations being linearly related to the timescale. The $1/f$ noise has been frequently observed in nature and in various biological phenomena, although the physiological mechanism behind remains speculative.

Examination of the DFA plot of heart rate has suggested the existence of two linear regions with different fractal slopes separated by a breakpoint n_{bp} [8]—the first region covered the range from 4 to n_{bp} beats, characterized by a short-term scaling exponent α_1; the second region covered the range from n_{bp} to 50 beats, characterized by a long-term scaling exponent α_2. As the previous infant study has found that the 8–15 beats range of heart period fluctuation appeared to provide most useful information in relation to IVH [20], n_{bp} was chosen to be 15. Therefore, the short-term scaling exponent α_1 was calculated from a window size of 4–15 beats, whereas the long-term scaling exponent α_2 was calculated from a window size of 15–50 beats.

The results for the cohort were presented as mean ± SD. Differences between the IVH and non-IVH infants were compared with the Student's t test. A P value of <0.05 was considered significant.

3 Results

The demographic and clinical characteristics of the studied infants are presented in Table 1. Out of the 30 infants studied, 26 infants were mechanically ventilated, 10 infants suffered from IVH and 2 infants died eventually (one infant did not suffer from IVH). Thus, there were 10 infants with IVH (9 of whom were ventilated) and 20 infants without IVH (17 of whom were ventilated) in our cohort. Note that there was no significant difference in the SBP, MAP, heart rate and CRIB II score (CRIB stands for Clinical Risk Index for Babies [7, 14]) between the two groups of infants. Out of the 16 infants excluded from the analysis, 3 infants suffered from IVH and 2 infants died eventually (one infant did not suffer from IVH).

The results from DFA of MAP, SBP and pulse interval are shown in Table 2 (for the whole group of infants) and in Table 3 (for the infants with mechanical ventilation). For both the short-term and long-term beat ranges, the regression fit R^2 was high (>0.9), which justified the validity of the DFA approach. The group averages of the DFA log–log plot for MAP in the short-term and long-term beat ranges are shown as Figs. 1 and 2, respectively. For the IVH infants, the short-term scaling exponents α_1 of both MAP and SBP were significantly higher than those of the non-IVH infants ($P = 0.017$ and $P = 0.038$,

Table 1 Physiological variables in the cohort of preterm infants

	IVH	Non-IVH	*P* value
Gestational age (weeks)	26.7 ± 1.7	26.9 ± 1.9	0.79
Birth weight (g)	1,023 ± 357	1,025 ± 340	0.99
CRIB II score	10 ± 3	10 ± 3	1
MAP (mmHg)	35.1 ± 6.0	35.2 ± 5.3	0.97
SBP (mmHg)	45.1 ± 9.6	43.6 ± 6.5	0.62
Heart rate (bpm)	139 ± 8	144 ± 10	0.11
Pulse interval (ms)	353 ± 146	402 ± 65	0.21

Values are mean ± SD

CRIB, clinical risk index for babies; SBP, systolic blood pressure; MAP, mean arterial pressure

respectively), and also closer to 1, that signifies 1/*f* fractal scaling. Similar results were seen in the infants with mechanical ventilation only ($P = 0.007$ and $P = 0.020$ for the α_1 of MAP and SBP, respectively). No significant difference was found between IVH and non-IVH in the long-term scaling exponent α_2 of MAP and SBP, and in both cases, α_2 appeared to be slightly above 1. No difference was found in either the short-term or long-term scaling exponents for pulse interval.

4 Discussion

This study is the first to examine the fractal dynamics of arterial BP in preterm infants using the DFA approach. The rationale was to address whether the fractal scaling of arterial BP could provide potentially useful information for distinguishing between preterm infants with and without brain hemorrhage. The main finding is that the short-term fractal scaling exponent α_1 is significantly higher in the IVH infants compared with the non-IVH infants. This finding suggests that fractal dynamics embedded in the arterial pressure waveform might hold important information that could allow early identification of preterm infants at risk of developing significant IVH after birth and led to further studies to examine ways of reducing the risk using this new information. In addition, the high R^2 (>0.9) in the DFA model fit provides validation to the appropriate use of this technique for analyzing fractal scaling in the BP fluctuation of infants.

The study of fractal scaling in arterial BP in adult humans using the DFA approach has revealed important contributions of the autonomic nervous system in the scaling exponents [4]. It was shown that blockade of vagal activity by atropine could lead to an increase in the short-term scaling exponent of BP. The main reason was believed to be the removal of heart rate variation that was being translated to BP fluctuation, specifically those generated by the respiratory modulation of cardiac vagal activity. As the heart beat intervals govern the period of diastolic decay in the arterial pressure pulse (the Windkessel mechanism) and also the diastolic filling of the heart (that determines stroke volume), they would have direct effects on DBP and SBP. Thus, smoother heart rate fluctuations could result in smoother BP fluctuations. Conversely, the administration of clonidine that causes central blockade of both cardiac and vascular sympathetic outflow and a central increase in cardiac vagal activity resulted in a decrease of the short-term BP exponent. The higher α_1 observed in the IVH infants might therefore be explained by either a reduction of vagal activity or an augmentation of sympathetic outflow compared with the non-IVH infants.

Table 2 Detrended fluctuation analysis (DFA) of MAP, SBP and PI in the cohort of preterm infants ($N = 30$)

	IVH ($N = 10$)		Non-IVH ($N = 20$)		*P* value	
	α_1	α_2	α_1	α_2	α_1	α_2
MAP						
α	1.06 ± 0.18	1.21 ± 0.16	0.84 ± 0.25	1.11 ± 0.19	0.017[a]	0.152
R^2	0.98 ± 0.02	0.97 ± 0.02	0.99 ± 0.01	0.98 ± 0.02	0.362	0.386
SBP						
α	0.98 ± 0.20	1.17 ± 0.15	0.78 ± 0.25	1.06 ± 0.21	0.038[a]	0.145
R^2	0.98 ± 0.01	0.97 ± 0.03	0.99 ± 0.01	0.97 ± 0.03	0.538	0.461
PI						
α	0.73 ± 0.35	1.06 ± 0.25	0.64 ± 0.37	0.96 ± 0.38	0.546	0.459
R^2	0.99 ± 0.01	0.97 ± 0.02	0.97 ± 0.03	0.95 ± 0.06	0.190	0.166

Values are mean ± SD

α_1, short-range scaling exponent (4–15 beats); α_2, long-range scaling exponent (15–50 beats); α, DFA scaling exponent; R^2, goodness of fit of the linear regression in DFA

[a] $P < 0.05$ between IVH and non-IVH

Table 3 Detrended fluctuation analysis (DFA) of MAP, SBP and PI in the cohort of preterm infants with mechanical ventilation ($N = 26$)

	IVH ventilated ($N = 9$)		Non-IVH ventilated ($N = 17$)		P value	
	α_1	α_2	α_1	α_2	α_1	α_2
MAP						
α	1.05 ± 0.18	1.22 ± 0.17	0.79 ± 0.23	1.09 ± 0.18	0.007[a]	0.093
R^2	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.01	0.631	0.756
SBP						
α	0.94 ± 0.17	1.16 ± 0.16	0.73 ± 0.22	1.03 ± 0.20	0.020[a]	0.092
R^2	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.02	0.928	0.871
PI						
α	0.66 ± 0.30	1.04 ± 0.26	0.66 ± 0.40	0.93 ± 0.41	0.970	0.482
R^2	0.99 ± 0.01	0.99 ± 0.01	0.99 ± 0.01	0.97 ± 0.03	0.201	0.146

Values are mean ± SD

α_1, short-range scaling exponent (4–15 beats); α_2, long-range scaling exponent (15–50 beats); α, DFA scaling exponent; R^2, goodness of fit of the linear regression in DFA

[a] $P < 0.05$ between IVH and non-IVH

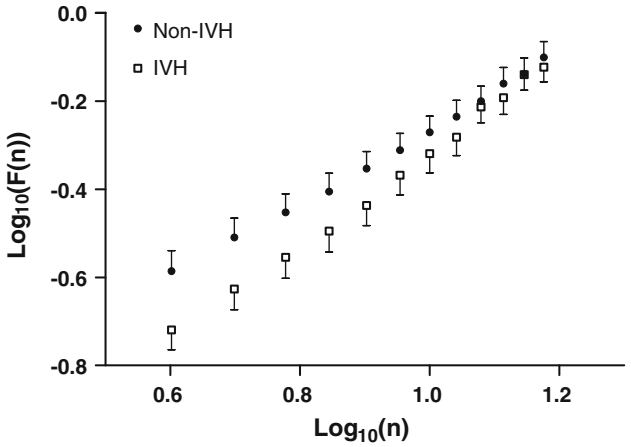

Fig. 1 The plot of $\log_{10}(F(n))$ versus $\log_{10}(n)$ from DFA of MAP for infants with IVH and those without (non-IVH), in the short-term beat range ($n = 4$–15 beats). The mean and SEM of the groups are shown. The short-term scaling exponents (α_1) are computed as the linear slopes of the individual plots

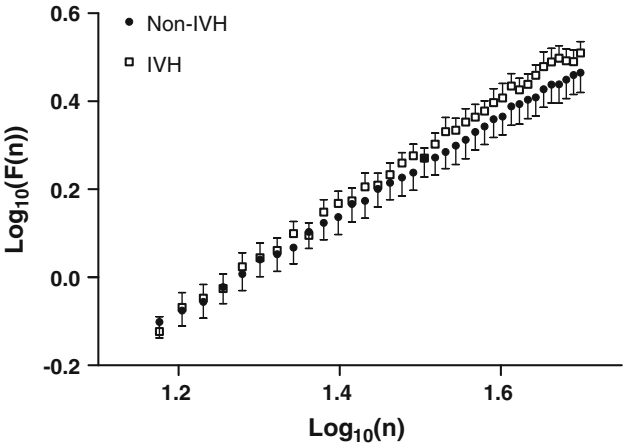

Fig. 2 The plot of $\log_{10}(F(n))$ versus $\log_{10}(n)$ from DFA of MAP for infants with IVH and those without (non-IVH), in the long-term beat range ($n = 15$–50 beats). The mean and SEM of the groups are shown. The long-term scaling exponents (α_2) are computed as the linear slopes of the individual plots

The use of mechanical ventilation was likely to be an important factor for the association between the short-term scaling exponent α_1 and IVH, given its influence on the respiratory fluctuation of BP and heart rate. In this cohort of preterm infants, a majority were breathing with mechanical ventilation (26 out of 30), and only a small number were breathing spontaneously (1 IVH and 3 non-IVH). The separate analysis performed on the mechanically ventilated subgroup showed similar results as the whole group (Table 3), with the IVH infants having higher α_1 than the non-IVH infants. In fact, the P values obtained were even smaller, and thus, it was possible that the use of mechanical ventilation could be a reason for the observed association between α_1 and IVH. Early studies have also strongly implicated the causal association of lack of patient to ventilator synchrony causing intraventricular hemorrhage [17, 18]. These studies occurred prior to the current methods of patient triggered ventilation and used paralytic agents to prevent adverse patient breathing interaction with the ventilator. Further prospective studies are planned with larger numbers to allow for statistical adjustment of the possible confounding effect of ventilation mode.

A previous study examined the use of DFA on the fluctuation of heart period (R–R) interval measured by electrocardiogram (ECG) in preterm infants suffering IVH [20]. The short-term scaling exponent (α_1) computed from the 8–15 beat range was found to be significantly higher in the infants who later developed IVH compared with those who did not. In the current study, the pulse interval extracted from the arterial BP waveform was used as a

measure of heart period fluctuation, but no significant difference was found between the IVH and non-IVH infants. A possible reason could be the difference between R–R interval variability and pulse interval variability, particularly in the high frequency range (respiratory frequency) [5], that corresponded to the timescale of the short-term exponent α_1.

Nevertheless, the higher α_1 found in the BP fluctuation of IVH infants was in agreement with the previous finding, both of which suggested a lack of vagal activity or an augmentation of sympathetic outflow compared with the non-IVH infants. Vagal nerve activity has been shown to play an important role in the regulation of cerebral blood flow during hemorrhage and cerebral ischemia [9]. Results from the current work have provided further evidence that development of IVH could involve impairment in parasympathetic outflow. However, the specific mechanism through which IVH is linked with vagal activity remains unclear thus far.

While it has been previously demonstrated that DFA of heart period (derived from ECG) could provide useful information for the identification of IVH [20], there are still potential benefits from the use of arterial BP. Firstly, it is not completely clear whether the fractal dynamics of arterial BP simply follow the heart period or represent additional mechanism that is not assessable from the DFA of heart period alone. Secondly, from the clinical viewpoint, it is not yet known which method may provide more relevant information for the detection of IVH, or whether the two methods can be applied together to improve the accuracy of detection. This would require further studies with simultaneous ECG and BP recordings in a larger cohort. Thirdly, it may be preferable to use arterial BP instead of ECG in situations where movement artifacts from the infants have led to degradation of ECG quality, such that sufficiently long artifact-free segments are not obtainable.

There are several advantages from deriving clinical information using the DFA method. Firstly, this method can be performed on an acceptable duration of data (10 min in this case), which is practical in the neonatal intensive care setting. Secondly, the information (namely the scale exponent) is derived from a specific beat range, which can be easily translated to a similar time range or frequency band used in other methods such as power spectrum analysis. This would largely facilitate the physiological interpretation of the derived parameters. Thirdly, it can be applied in conjunction with the commonly used spectral analysis method to provide a more complete picture of the underlying cardiovascular dynamics, as both methods can provide complementary information [4].

There are some limitations to this study. Firstly, due to the relatively low incidence of IVH in our cohort, it was not possible to assess how the DFA exponents relate to the severity of hemorrhage. Secondly, the data duration of 10 min placed a limitation on the longest beat range that can be assessed by DFA. It would be desirable that these limitations could be overcome in future by improvement in the experimental design.

In conclusion, this study examined whether the application of DFA on the arterial BP signal could derive markers for the identification of preterm infants who developed IVH. The results showed that the IVH infants had higher short-term scaling exponents of both MAP and SBP compared to the non-IVH infants. Thus, fractal dynamics in arterial BP could provide potentially useful information that facilitates early identification of IVH in preterm infants.

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