Long-term HRV in critically ill pediatric patients: comma versus brain death

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Abstract

Dysfunctions of the autonomic nervous system in critically ill patients with Acute Brain Injury (ABI) lead to changes in Heart Rate Variability (HRV) which appear to be particularly marked in patients subsequently declared in Brain Death (BD). HRV series are non-stationary, exhibit long memory in the mean and time-varying conditional variance (volatility), characteristics that are well modeled by AutoRegressive Fractionally Integrated Moving Average (ARFIMA) models with Generalized AutoRegressive Conditional Heteroscedastic (GARCH) errors. The long memory is estimated by the parameter d of the ARFIMA-GARCH model, whilst the time-varying conditional variance parameters, u and v characterize, respectively, the short-range and the persistence in the conditional variance. In this work, the ARFIMA-GARCH approach is applied to HRV series of 15 pediatric patients with ABI admitted in a pediatric intensive care unit, 5 of which has BD confirmed and 9 patients survived. The long memory and time-varying conditional variance parameters estimated by ARFIMA-GARCH modeling significantly differ between groups and seem able to contribute to characterize disease severity in children with ABI.

1. Introduction

Dysfunctions of the autonomic nervous system in critically ill patients with Acute Brain Injury (ABI) lead to changes in Heart Rate Variability (HRV) which appear to be particularly marked in patients subsequently declared in Brain Death (BD). Previous studies on cardiovascular series variability indicate that the derived indexes can not only provide a complementary tool for time course prediction and prognostic in critical illness, but also lead to early reliable predictors of BD, contributing for the efficiency of organ transplantation programs [1, 2]. It is well known that reduced HRV, assessed in time, frequency and complexity, is a risk index after trauma for both morbidity and mortality and an early predictor of BD. Although some authors have proposed HRV as an auxiliary tool in trauma triage, it is neither used in the clinical practice for ABI patients, nor considered in the guidelines for BD determination [2–4]. HRV series are non-stationary, exhibit long memory in the mean and time-varying conditional variance, characteristics that are well modeled by AutoRegressive Fractionally Integrated Moving Average (ARFIMA) models with Generalized AutoRegressive Conditional Heteroscedastic (GARCH) errors. The long memory is estimated by the parameter d of the ARFIMA-GARCH model, whilst the time-varying conditional variance parameters, u and v characterize the short-range and the persistence, respectively, in the conditional variance. Previous studies [5] indicate that for normal subjects these parameters show circadian variation: the parameter d has lowest values, $0 < d < 0.5$, during the night period with mean (std) $0.35\ (0.05)$ and the parameters $u,\ v$ present, for the same period, values of $0.17\ (0.06)$ and $0.64\ (0.05)$, respectively, indicating persistence in the conditional volatility. This work applies the ARFIMA-GARCH approach to HRV series of 15 pediatric patients with ABI admitted in a pediatric intensive care unit with the aim of contributing to the characterization of the HRV in these patients and early brain death assessment.

2. ARFIMA-GARCH models

ARFIMA$(p, d, 0)$-GARCH$(1, 1)$ models are defined as follows

$$\phi(B)(1-B)^d x_t = \epsilon_t, \tag{1}$$

$$\epsilon_t = \sigma_t z_t, \qquad \sigma_t^2 = w + v\sigma_{t-1}^2 + u\epsilon_{t-1}^2 \tag{2}$$

where B is the backward-shift operator, $(1-B)^d = \sum_{k=0}^{\infty} \binom{d}{k} (-1)^k B^k$ is the fractional difference operator [5], $d \in \mathbb{R}$, $p \in \mathbb{N}$, $\phi(B) = 1 - \phi_1 B - ... - \phi_p B^p$ is

the autoregressive polynomial (in B), $w > 0$, $v, u \geq 0$, $u + v < 1$, and z_t are independent and identically distributed random variables with zero mean and unit variance.

Equation (1) describes the conditional mean of the process with parameter d determining the long-term behaviour in the mean, whereas p and the coefficients in $\phi(B)$ allow for the modeling of the processes short-range properties. The model is stationary for $-0.5 < d < 0.5$ but mean reverting for $0.5 \leq d < 1$. The long memory parameter is related to the Hurst coefficient, $H = d + 0.5$, to the fractal dimension, $D = 2 - H$ and to the slope of the (generalized) spectral density in the low frequency range by $\alpha = 2d$, [5, 6].

Equation (2) describes the dynamics of the conditional variance (volatility) of the process: σ_t^2 is dependent on its own lagged values and on the squared residuals of the mean equation. The parameter u characterizes the short-range properties in the volatility and the parameter v characterizes the persistence in the volatility. This model encompasses the classic short-memory AR(p) model, for $d = u = v = 0$, the long memory ARFIMA$(p, d, 0)$ model, for $u = v = 0$ and the ARFIMA$(p, d, 0)$-ARCH(1) model, for $v = 0$.

Given a time series $x_1, \ldots, x_n$, to estimate the parameters of an ARFIMA$(p, d, 0)$-GARCH(P, Q), $P, Q \in \{0, 1\}$ model proceed as follows, [5]:

1. estimate d using the semi-parametric local Whittle estimator;
2. define the filtered data $y_t = (1 - B)^d x_t$;
3. estimate the AR(p)-GARCH(P, Q) parameters in the filtered data y_t.

In step 3, AR(p)-GARCH(P, Q) parameters are estimated by maximum likelihood with initial parameters obtained by least squares and the order p of the AR component determined by the Akaike Information Criterion (AIC). The conditional heteroscedasticity in the series is assessed by the Ljung-Box test in the squared residuals, [7]. In the presence of heteroscedasticity and to keep the model parsimony an AR(p)-GARCH(1,0) or AR(p)-ARCH(1) model is first considered, in this work. If the series does not present heteroscedasticity then the final model is an ARFIMA$(p, d, 0)$.

As usual only models for which the residuals are not correlated, checked by the Ljung-Box test for the residuals, are considered valid models.

3. Data and pre-processing

This study considers 15 pediatric patients with acute brain injury admitted in the Pediatric Intensive Care Unit (PICU) of Centro Hospitalar S. João, Porto, Portugal. The patients are part of a database collected at PICU between 2006 and 2011, in a project approved by the respective ethic commission and by the Portuguese data protection authority. Parents gave signed informed consent for inclusion of their children in the database. The cases were selected by age criteria (11-14 years old) and by the availability of a high resolution 12-lead ECG Holter recording with a minimum duration of 3 hours. Brain death has been confirmed for 5 patients (D1-2, D4-6) during the recording or at a latter moment by the usual protocol. One patient died during the recording (also included in the BD group as D3), while the remaining 9 patients Survived (S1-S9). ECG leads I, III, V1-V6 were automatically delineated using the wavelet transform based system described in [8] and the R peak taken as the median mark of the single lead. The beat-to-beat RR series obtained from these marks were then filtered for ectopic and artifact correction.

4. HRV modeling

Given the long HRV record the procedure is as follows. First a selective adaptive segmentation decomposes the long record into short excerpts of variable length (minimum of 400 beats and maximum of 3000 beats) by finding structural breaks in the mean persistence using the ARFIMA model, equation (1), as described in [5]. PICU HRV data often present severe outliers that are not removed by the usual preprocessing and hinder the modeling of the segments. Consequently segments containing RR out of the band given by the median filter on a 100-points window ± 2 RR standard deviation are not admissible for the subsequent analysis. For each admissible RR segment: test the null hypothesis that there are unit roots (Augmented-Dickey-Fuller test, [9]) in which case, $d \geq 1$, and a stationary or mean reverting model is estimated for the RR increments or first differenced series, ΔRR. Long-range correlations and conditional volatility are then assessed in each segment by the ARFIMA-GARCH modeling as described in section 2.

The approach is illustrated in figure 1 for an excerpt of 7 segments of patient S7 recording (with the break points identified by the vertical lines), along with the estimated parameters, d, u, v, the indication of the type of model for each segment, the ARFIMA model residuals and the conditional standard deviation. The figure illustrates how distinct RR segments are modeled by different models and how the estimated parameters vary in time, e.g. for the first segment $d = 0$ (meaning no long memory) while for the remaining segments $d = 0.40,\ 0.22,\ 1,\ 1.23,\ 0.31,\ 0.79$ indicating strong persistence in the mean. Regarding the conditional volatility, the first segment shows some weak non-persistent volatility ($u = 0.14, v = 0$) and absence of conditional volatility in segments 2, 3 and 4 ($u = v = 0$). Finally for segments 5, 6 and 7 $u = 0.16, 0.09, 0.12$ and $v = 0.84, 0.88, 0.81$, respectively, indicating strong persistence in conditional volatility in accordance with the

volatility clusters in the ARFIMA residuals. The changes in u and v are well represented in the lower panels which illustrate how the fitted model captures the increased clustered variability in the last segment.

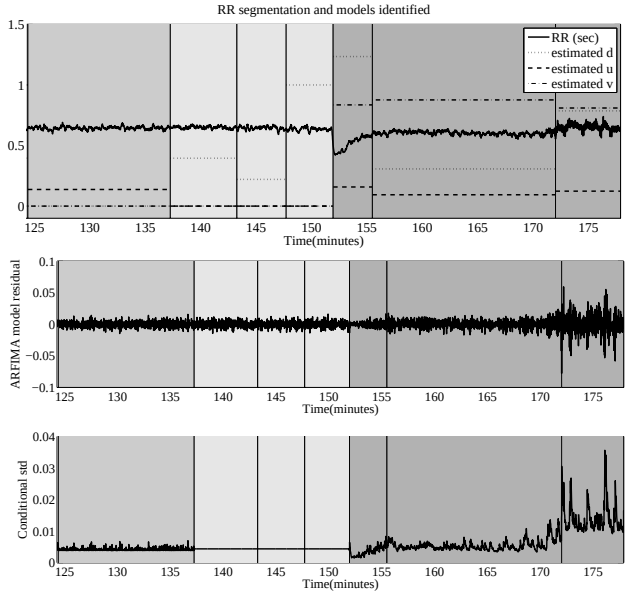

Figure 1. Example of ARFIMA-GARCH modeling for patient S7. Represented segments delimited by vertical lines with background increasing grey scale indicating chosen model: ARFIMA, ARFIMA-ARCH, ARFIMA-GARCH.

5. Results and discussion

The methodology described and illustrated in section 4 is applied to the 15 patients and two key results are analysed: the type of model, ARFIMA, ARFIMA-ARCH, ARFIMA-GARCH predominating in each group and the distribution of the parameters.

Figures 2 and 3 summarize the results only for valid segments for which an adequate model was found. The results are normalized by the number of beats in the segment so that the different segment lengths are accounted for. The percentage of each type of model per patient is represented in the figure 2 with the grey scale indicating models of increasing complexity. The darkest grey tone indicates that neither ARCH nor GARCH was able to model the heterocedasticity in the ARFIMA residuals. The heterocedasticity is equally predominant in both groups but a significantly (5%) lower percentage of beats required $v > 0$ (ARFIMA-GARCH model) in the D group (10% of all beats in group) when compared with S group (40%). This indicates a different behavior of the conditional variance in the groups.

Regarding the distribution of the parameters, figure 3 indicates that it is also different between the groups. For d, figure 3(a) the two groups were found to have statistical differences (5% MannWhitney U test), with means (standard deviation) of respectively 0.44 (0.25) and 0.84 (0.25). Typical d values for the S group are lower than 0.8; for group D, in 5 (out of 6) patients, $0.5 \leq d < 1$ (shaded in figure and corresponding to mean reverting ARFIMA models) for the 50% of the beats lying between the first and third quartiles. Higher d values for patient D3 may reflect the fact that he entered cardiac arrest without BD confirmation.

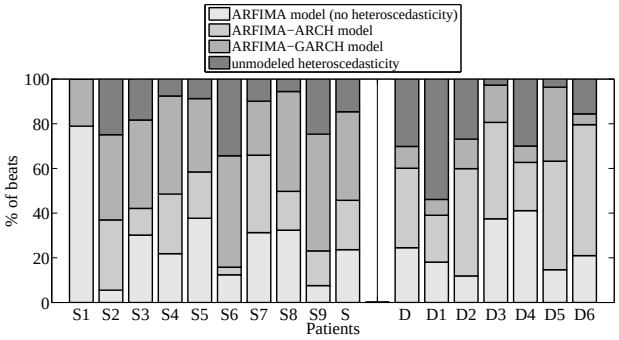

Figure 2. Distribution of model types (%) per patient; S and D stand for global results of all patients in the group.

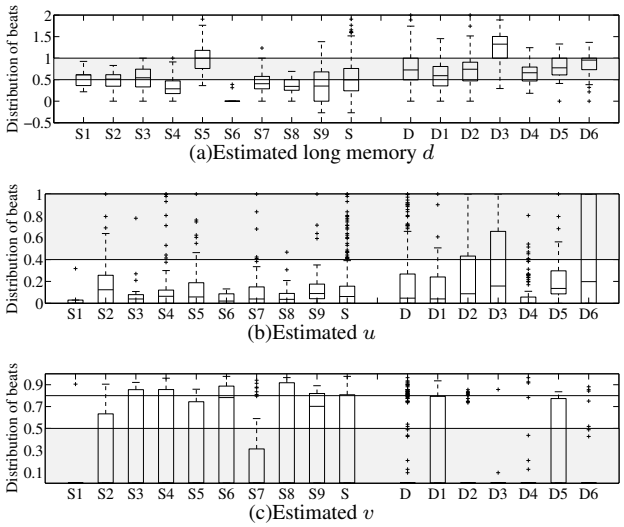

Figure 3. Boxplots for d (a), u (b) and v (c) per patient; S, D - global results of all patients in the group.

In figure 3(b) and 3(c) the shaded areas represent typical values found for group D with limits computed as mean+[−]3std for u[v] over normal patients during sleep found in [5]. The values for u are higher for D group, with a mean of 0.31 (0.13) than for S group with a mean of 0.14 (0.10) while v is higher for the S group, 0.38 (0.14) than for D group 0.12 (0.08), with a percentage of 85% of null

values. As a matter of fact, for 4 out of 6 D cases, and none for S group, less than 25% of the beats required an ARFIMA-GARCH model ($v > 0$). The distribution of u and v are statistically different at 5% and 0.5% levels, respectively. Clearly, the D group presents a higher (lower) percentage of ARFIMA-GARCH segments with $u > 0.4$ ($v < 0.5$) (shaded areas), indicating absence of persistence in the volatility. Recall that for this group D the fraction of segments requiring the ARFIMA-GARCH model is lower reflecting the different variance behavior.

6. Conclusions

The long memory and time-varying conditional variance parameters estimated by ARFIMA-GARCH modeling seem able to contribute to characterize disease severity in ABI children. For non survivors (D group) the values of $0.5 \leq d < 1$ indicate less stability in mean HRV. Additionally lower persistence in volatility was noticed, with 90% of beats modeled with non-persistent ($v = 0$) volatility.

The results indicate that persistence in volatility may be used to discriminate between S and D and that the potential of parameter v as early indicator of brain death should be explored.

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