Exploring QT Variability Dependence from Heart Rate in Coma and Brain Death on Pediatric Patients

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Abstract

Patients with acute brain injury (ABI) present dysfunctions of the autonomic nervous system and consequent alterations on the cardiac parameters, particularly in brain death (BD). Therefore the study of cardiovascular variabilities can provide a complementary tool for time course predicting and prognostic. QT variability (QTV) versus heart rate variability (HRV) interactions were explored using a low order AR-ARARX model, previously validated, which allows quantifying the QTV Fraction ($F\%$) driven by HRV. High resolution 12-lead ECG Holter recordings were taken from pediatric patients admitted to the intensive care unit with ABI. Power of HRV and QTV driven and undriven fractions were calculated considering the frequency bands: $< 0.04Hz$ (VLF), $0.04-0.15Hz$ (LF), $0.15-0.4Hz$ (HF), $> 0.4Hz$ (HF+) and all frequencies (TP). The median of $F\%$ in patients for which BD has been confirmed was found to be significantly lower in TP, VLF and HF bands and significantly higher in HF+ ($p< 0.005$). Uncoupling of QT vs RR have clinical potential in differentiating the progression of the disease within children with ABI, and can contribute for a better individual adjustment in treatment type and timing, and as early prognostic predictor of BD.

1. Introduction

Patients with acute brain injury (ABI) present dysfunctions of the autonomic nervous system (ANS) that produce alterations on the cardiac parameters, particularly in patients for whom brain death (BD) is confirmed subsequently. The study of cardiovascular series variabilities can not only provide a complementary tool for time course predicting and prognostic, but moreover can lead to early reliable predictors of BD, contributing for the efficiency of organ transplantation programs.

It is well known that reduced heart rate variability (HRV), accessed in time, frequency and complexity, is a risk index after trauma, for both morbidity and mortality, and an early predictor of BD. Some authors have proposed HRV as auxiliary tool in trauma triage, nevertheless HRV is not yet used in the clinical practice for ABI patients, neither considered in the guidelines for BD determination [1, 2]. Some intracranial events, as hemorrhage and traumatic brain injury (TBI) can induce cardiac abnormalities in ECG morphology and rhythm, namely in T wave morphology and QT interval prolongation [3,4]. Thus QT variability (QTV) and its HRV dependence are likely to be also affected.

Study QTV and HRV relation over clinical ECG data is a trick task, due to uncertainty in T wave delineation in the presence of noise. The effect over ANS and cardiac function of several drugs used in intensive care, as dopamine, noradrenaline, vecuronium, fentanil, propofol or the midazolam, and the different causes of the ABI (TBI, infection, anoxia, etc...) are additional difficulties to consider. Also, with respect to pediatric patients which physiology differs from adult patients the range of ages is an important aspect to take into account.

In this work a parametric approach is used for exploring the short time linear dependency of QTV on HRV extracted from Holter recordings of pediatric patients with ABI, some of which with BD outcome. The HRV, QTV and the QTV fraction driven by HRV are quantified and compared among patients with different outcome and in records from same patients at different times, aiming to find changes in QTV vs HRV relation related to the severity of the illness.

2. Data and methods

High resolution 12-lead ECG Holter recordings from 16 pediatric patients with acute brain injury (ABI) admitted

in the pediatric intensive care unit of Centro Hospitalar S. João (Portugal) were considered in this study. These data are integrated of a larger database (45 cases) collected at the Pediatric intensive care unit of the university hospital (Centro Hospital de S.João) between 2006 and 2011, in a project approved by the respective ethic commission and by the portuguese data protection authority. Parents have given signed informed consent for inclusion of their children in the database. Cases used in this study were selected by age criteria (11-14 years old) and include 6 patients for which brain death (BD) has been confirmed by the usual protocol, during the recording or in a latter moment; all the other have survived (S).

ECG recordings were automatically annotated using a wavelet-based system previously developed and validated [5]. Each of the 8 leads (I, II and V1 to V6) was independently annotated (SL marks) and an unique set of marks was obtained as the median mark for R wave peak and the first[last] QRS onset[T wave end] among leads with 2 more SL marks in a 12 msec neighborhood. The interval $RR(n)$ related to the n^{th} beat is defined as the time from $(n-1)^{\text{th}}$ to the n^{th} beat, and $QT(n)$ refers to the QT interval in the n^{th} beat, according with the final marks. In both series, any time interval out of the 3 standard deviations of all series or out of the 1.5 standard deviations of the moving median in a 50 samples interval is considered to be an outlier and excluded. Segments of 250 consecutive beats without missing QT intervals or outliers in any of the series are considered and a notch filter at 0Hz was applied in each segment for detrending.

QTV versus HRV interactions were explored over these segments using a low order AR-ARARX model as described in [6]. This method explores the beat-to-beat dependency of repolarization, quantifying the QTV Fraction linearly driven by HRV (F %). It assumes an open loop linear model (Fig. 1) where $x_{\text{RR}}(n) = RR(n) - T_{\text{R}}$ and $x_{\text{QT}}(n) = QT(n) - T_{\text{QT}}$ are the interval series corrected for the mean (T_{R} and T_{QT} the mean RR and QT, respectively,in the analyzed segment); $w_{\text{RR}}(n)$ and $w_{\text{QT}}(n)$ are uncorrelated stationary zero-mean white noises with standard deviations λ_{RR} and λ_{QT}, $A_{22}(z)$ is an order p polynomial and $A_{11}(z)$, $A_{12}(z)$, $D(z)$ are polynomials with order q. Thus, the series $x_{\text{RR}}(n)$ is modeled as an order p autoregressive stationary random process (AR_p), while the QTV trend, $x_{\text{QT}}(n)$, is assumed to result from two uncorrelated sources, one driven by HR and one resulting from other input ($ARARX_q$), as schematized in Fig. 1.

The assumption of uncorrelated sources allows to compute the power spectral density (PSD) of $x_{\text{QT}}(n)$ as the sum of the partial spectra that express the contributions related and unrelated to HRV. The spectral power within a given frequency can be obtained by summing the contributions of the poles located in the band. Power of HRV ($P^{\mathcal{B}}_{\text{RR}}$), QTV

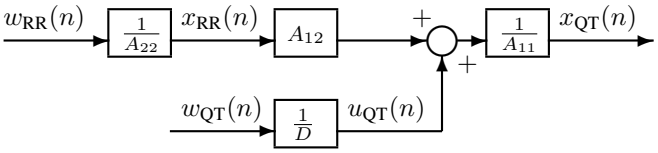

Figure 1. Model of QTV versus HRV interactions.

fractions (RR related: $P^{\mathcal{B}}_{\text{QT|RR}}$, RR unrelated: $P^{\mathcal{B}}_{\text{QT|QT}}$) and global QTV ($P^{\mathcal{B}}_{\text{QT}}$)were calculated over valid models considering the frequency bands $\mathcal{B}$: < 0.04 (VLF), $0.04-0.15$ (LF), $0.15-0.4$ (HF), > 0.4Hz (HF+) and all frequencies (TP). The relative fraction of the QTV driven by RR in a frequency band $F(\mathcal{B})\%$ is given as the following ratio:

$$F^{\mathcal{B}}\% = \frac{P^{\mathcal{B}}_{\text{QT|RR}}}{P^{\mathcal{B}}_{\text{QT|RR}} + P^{\mathcal{B}}_{\text{QT|QT}}} \times 100 = \frac{P^{\mathcal{B}}_{\text{QT|RR}}}{P^{\mathcal{B}}_{\text{QT}}} \times 100. \quad (1)$$

A Wilcoxon rank test for equality of medians was applied to compare S and BD groups.

3. Results and discussion

Valid models were obtained for 1263 and 361, respectively for S and BD groups, allowing to include in the analysis a total of 12 patients, as described in Table 1.

The median spectral power by frequency band of HRV, QTV and QTV fractions is presented in Table 2, along with the majorant for the p-value of the correspondent statistical test. As expected BD group presented reduced HRV in all frequency bands, with high significance ($p < 10^{-16}$). With respect to QTV, significative lower measures were also found for VLF and HF, but the power in HF+ and TP was increased. Analogous results were found analyzing separately the power in each QTV fraction, except for a non significative decrease of $P^{\mathcal{B}}_{\text{QT|RR}}$.

The distribution of $F^{\mathcal{B}}\%$ for each frequency band in both S and BD groups is presented in the Fig 2; the median values and respective majorant for the p-value are presented in Table 3. F% in BD group was significantly lower for TP, VLF and HF bands and significantly higher for HF+ ($p < 0.005$). Thus regarding all frequencies (TP), in spite of increased power in both QTV fractions in BD group, the relative importance of the QTV linearly driven by HRV is decreased. This result suggests that the two QTV fractions are affected in a different manner, resulting in uncoupling of ventricular repolarization with heart rate. Moreover for 4 patients that survived and for which data is available within a few days apart, median F% has increased considering TP, what can reflect an improvement in the patient state. On the hand hand, for the only patient in Brain death group for which two recordings at different days were included in the analysis, median F% has increased both for TP and HF, decreasing for HF+. Ac-

Table 1. Patients included in the study

	Survivals	Brain Death
	7	5
# segments	1263	361
non TBI	0	4
TBI	7	1

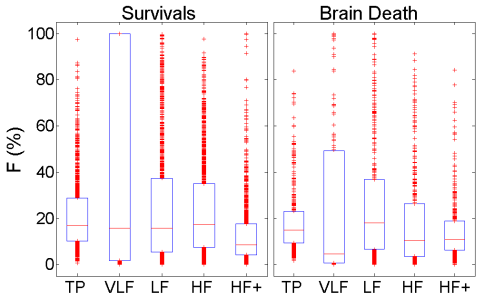

Figure 2. F% distribution (box and whisker plots) for S and BD groups.

cording with the clinical information of this patient, brain death testing protocol has been initiated at the day of the first recording with negative results in apnea testing, as the patient reveals signs of spontaneous breathing. A second brain death test has been performed at the day of the second recording, this time with a positive result what confirmed the brain death. Thus the clinical state of the patient is consistent with an evolution from comma to brain death, confirming the conclusions that can be taken from the spectral measures.

The use of an homogeneous age criteria for selecting patients (11-14 years old) allowed to avoid the problem of dealing with different ages, but resulted in a small data set to be used. In particular, it was not possible to consider the effect of the different causes of the ABI in this dataset, as all non TBI cases were in the BD group. That configures the main limitation of this work. With respect to the drugs confusing effect, both groups includes patients under the some kind of substances, with a higher level of sedoanalgesia over survivals. Sedation and analgesia, inducing comma, can reduce HRV and thus the values of the parameters on those patients should be closer to the the values in the BD group, reducing the differences between groups. Nevertheless, the results allowed to differentiate S and BD groups.

4. Conclusions

Uncoupling of QT/RR has clinical potential in differentiating the progression of the disease and the outcome within children with ABI. Further studies should be performed to establish the effect of the cause of the ABI and sedoanalgesia over the parameters and to determine cut-off points that could constitute an auxiliary clinical tool for providing a better individual adjustment in treatment type and timing and early prognostic predictor of BD.

Table 2. Median of spectral power measures and p-values

	Survivals	Brain Death	p value
HRV			
$P_{\text{RR}}^{\text{TP}}$	$148,6$	$23,3$	$< 10^{-4}$
$P_{\text{RR}}^{\text{VLF}}$	$7,5E-04$	$0,0$	$< 10^{-4}$
$P_{\text{RR}}^{\text{LF}}$	$54,0$	$8,0$	$< 10^{-4}$
$P_{\text{RR}}^{\text{HF}}$	$18,4$	$1,5$	$< 10^{-4}$
$P_{\text{RR}}^{\text{HF+}}$	$6,0$	$2,7$	$< 10^{-4}$
QTV			
$P_{\text{QT}}^{\text{TP}}$	$13,3$	$14,8$	$< 10^{-3}$
$P_{\text{QT}}^{\text{VLF}}$	$1,6E-06$	$6,2E-07$	$< 10^{-4}$
$P_{\text{QT}}^{\text{LF}}$	$1,6$	$1,7$	no significance
$P_{\text{QT}}^{\text{HF}}$	$6,0$	$4,6$	$< 10^{-4}$
$P_{\text{QT}}^{\text{HF+}}$	$4,3$	$7,8$	$< 10^{-4}$
$P_{\text{QT\|RR}}^{\text{TP}}$	$2,1$	$2,0$	no significance
$P_{\text{QT\|RR}}^{\text{VLF}}$	$1,2E-07$	$1,2E-08$	$< 10^{-4}$
$P_{\text{QT\|RR}}^{\text{LF}}$	$0,2$	$0,2$	no significance
$P_{\text{QT\|RR}}^{\text{HF}}$	$1,0$	$0,4$	$< 10^{-4}$
$P_{\text{QT\|RR}}^{\text{HF+}}$	$0,3$	$0,8$	$< 10^{-4}$
$P_{\text{QT\|QT}}^{\text{TP}}$	$10,7$	$12,4$	$< 10^{-4}$
$P_{\text{QT\|QT}}^{\text{VLF}}$	$7,0E-07$	$4,7E-07$	$< 10^{-4}$
$P_{\text{QT\|QT}}^{\text{LF}}$	$1,2$	$1,17$	no significance
$P_{\text{QT\|QT}}^{\text{HF}}$	$4,6$	$3,9$	$< 10^{-3}$
$P_{\text{QT\|QT}}^{\text{HF+}}$	$3,9$	$6,8$	$< 10^{-4}$

Table 3. Median of $F(\mathcal{B})\%$ and p-values

	Survivals	Brain Death	p value
$F^{\text{TP}}\%$	17.12	14.95	$< 10^{-2}$
$F^{\text{VLF}}\%$	15.84	4.70	$< 10^{-4}$
$F^{\text{LF}}\%$	15.88	18.00	no significance
$F^{\text{HF}}\%$	17.52	10.42	$< 10^{-4}$
$F^{\text{HF+}}\%$	8.61	10.79	$< 10^{-2}$

Acknowledgments

CMUP research funded by the European Regional Development Fund through the programme COMPETE and by the Portuguese Government through the FCT - Fundação para a Ciência e a Tecnologia under the project PEstC/MAT/UI0144/2011. CIBER-BBN is an initiative funded by the VI National R&D&i Plan 2008-2011, Ini-

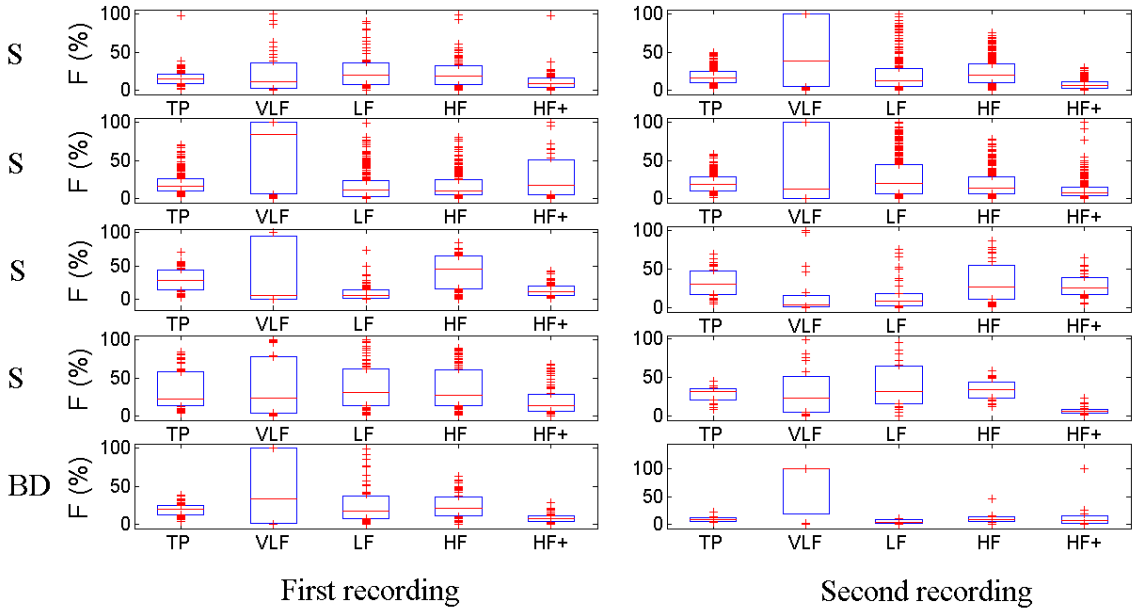

Figure 3. F% distribution (box and whisker plots) at different moments for 5 patients.

ciativa Ingenio 2010, Consolider Program, CIBER Actions and financed by the Instituto de Salud Carlos III with assistance from the European Regional Development Fund. This study was partially supported by project TEC2010-21703-C03-02 from the Ministerio de Economia y Competitividad (MINECO) with European Regional Development Fund, Spain, and Grupo Consolidado GTC T30, from Gobierno de Aragón, Spain. Authors acknowledge the support from Mortara Instr Inc., represented in Portugal by CardioSolutions, Lda.

References

[1] Ryan ML, Thorson CM, Otero Ca, Vu T, Proctor KG. Clinical applications of heart rate variability in the triage and assessment of traumatically injured patients. Anesthesiology research and practice January 2011;2011(January 1997):416590. ISSN 1687-6970.

[2] Nakagawa Ta, Ashwal S, Mathur M, Mysore M. Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations-executive summary. Annals of neurology April 2012;71(4):573–85. ISSN 1531-8249.

[3] Perron aD, Brady WJ. Electrocardiographic manifestations of CNS events. The American journal of emergency medicine October 2000;18(6):715–20. ISSN 0735-6757.

[4] Plymale J, Park J, Natale J, Moon-Grady A. Corrected QT Interval in Children With Brain Death. Pediatric cardiology October 2010;31(7):1064–9. ISSN 1432-1971.

[5] Martínez JP, Almeida R, Olmos S, Rocha AP, Laguna P. Wavelet-based ECG delineator: evaluation on standard databases. IEEE Transactions on Biomedical Engineering 2004;51:570–581.

[6] Almeida R, Gouveia S, Rocha AP, Pueyo E, Martínez JP, Laguna P. QT variability and HRV interactions in ECG: Quantification and reliability. IEEE Transactions on Biomedical Engineering 2006;53:1317–1329.

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