

# Heart rate variability predicts 30-day all-cause mortality in intensive care units

David G Bishop<sup>ab\*</sup>, Robert D Wise<sup>ab</sup>, Carolyn Lee<sup>ab</sup>, Richard P von Rahden<sup>ab</sup> and Reitze N Rodseth<sup>abc</sup>

<sup>a</sup>Perioperative Research Group, Pietermaritzburg Metropolitan Department of Anaesthetics, Critical Care and Pain Management, Pietermaritzburg, South Africa

<sup>b</sup>Nelson R. Mandela School of Medicine, Discipline of Anaesthesia and Critical Care, University of KwaZulu-Natal, Durban, South Africa

<sup>c</sup>Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

\*Corresponding author, email: davidgbishop@gmail.com

**Background:** Autonomic nervous function, as quantified by heart rate variability (HRV), has shown promise in predicting clinically important outcomes in the critical care setting; however, there is debate concerning its utility. HRV analysis was assessed as a practical tool for outcome prediction in two South African hospitals and compared with Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring.

**Method:** In a dual centre, prospective, observational cohort study of patients admitted to the intensive care units (ICU) of two hospitals in KwaZulu-Natal, South Africa frequency domain HRV parameters were explored as predictors of all-cause mortality at 30 days after admission; ICU stay duration; the need for invasive ventilation; the need for inotrope/vasopressor therapy, and the need for renal replacement therapy. The predictive ability of HRV parameters against the APACHE II score for the study outcomes was also compared.

**Results:** A total of 55 patients were included in the study. Very low frequency power (VLF) was shown to predict 30-day mortality in ICU (odds ratio 0.6; 95% confidence interval 0.396-0.911). When compared with APACHE II, VLF remained a significant predictor of outcome, suggesting that it adds a unique component of prediction. No HRV parameters were predictive for the other secondary outcomes.

**Conclusion:** This study found that VLF independently predicted all-cause mortality at 30 days after ICU admission. VLF provided additional predictive ability above that of the APACHE II score. As suggested by this exploratory analysis larger, multi-centre studies seem warranted.

**Keywords:** APACHE II, autonomic nervous system, critical care, heart rate variability, mortality

## Introduction

Heart rate variability (HRV) is a tool used to assess central nervous system autonomic function and guidelines for its use have been in place for almost 20 years.<sup>1</sup> HRV analysis has shown promise in predicting clinically relevant outcomes in the critical care setting, to risk stratify patients,<sup>2</sup> and predict outcomes such as mortality<sup>3</sup> and multiple organ dysfunction syndrome (MODS).<sup>3,4</sup> Enhanced outcome prediction may enable better resource allocation and potentially assist with end-of-life decisions. Our primary objective was to assess HRV analysis as a practical tool for outcome prediction and to compare it to Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring. We complied with the STROBE statement standards in the reporting of this observational study.<sup>5</sup>

## Materials and methods

### Study design

We undertook a dual-centre, prospective, observational cohort study of patients admitted to the intensive care units (ICU) of two hospitals providing regional and tertiary level services in KwaZulu-Natal, South Africa. Ethical approval for the study was given through the University of KwaZulu-Natal Bio-ethics Committee (BE 414/14), and permission to conduct the study was given by the management of both hospitals and the national Department of Health.

### Patients and setting

Our investigation was a sub-study of a multi-centre outcomes study that included both ICUs (30DOS: 30-day outcome study of

patients in intensive care units in KwaZulu Natal [BE 210/14]). Consent to use patient data fell under this broader study. A convenience sampling method was used, which limited the total number of eligible patients to the time-frame of the parent study. Patients 18 years of age or older that were admitted to Edendale or Grey's Hospital ICUs over a four-week period (October 20, 2014 to November 14, 2014) were considered eligible. This time period was selected to ensure a representative patient sample by avoiding school holidays and therefore a possible bias toward trauma patients. Eligible patients had a Holter taken within 24 hours of admission between 10h00 and 13h00. The ethics committee waived the need for consent as Holter analysis is routine in these ICUs. Patients were excluded if they: were not admitted during the study time period; did not have a Holter of at least five minutes' duration; were not in sinus rhythm; had artefacts or ectopic beats in more than 2% of their recording; or were lost to follow-up. Patients were followed up for 30 days after initial admission and those discharged from hospital were contacted telephonically.

### HRV analysis

Holter recordings were done with Schiller Holters (MT-101) (Schiller AG, Baar, Switzerland) and analysed using Schiller MT-200 software. Holters were CF classified (safe for direct cardiac application) and met the standards required for ECG recordings to be used in HRV analysis, as laid out by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.<sup>1</sup> Initial Holter analysis was done manually to confirm sinus rhythm. The first five-minute segment

of the Holter recording was used for analysis, provided the segment met ECG criteria for inclusion. Five-minute recordings are recommended for short-term frequency domain analysis.<sup>1</sup> We excluded any patient who had a recording of less than five minutes, as VLF power measurements are less reliable in shorter recordings. Intervals between successive beats (RR intervals) were then exported to the HRV software analysis program, Kubios© version 2.2 (Department of Applied Physics, University of East Finland; available at <http://kubios.uef.fi/>). All Holter analyses were performed by the corresponding author.

The specific analysis of heart rate variability is complex. Broadly speaking, there are three categories of analysis: time-domain, frequency domain and non-linear. We used frequency domain analysis because it can be calculated from relatively shorter ECG recordings, which makes it more practical. Frequency domain methods employ power spectral density analysis, which assesses how variance is distributed as a function of frequency.<sup>1</sup> This is further divided into parametric and non-parametric methods. We used a non-parametric method (fast Fourier transformation), which uses a simpler algorithm, has a higher processing speed and allows for easier post-processing of the spectrum.<sup>1</sup> Practically these calculations are done through software packages, such as the Kubios© software we used in this study. There are several reviews available on this topic for interested readers.<sup>1,6,7</sup>

### Outcomes

The primary outcome was the assessment of frequency-domain HRV parameters as a predictor of all-cause mortality at 30 days following ICU admission. Frequency domain analysis is one of the more commonly used techniques for analysis of HRV, using Fourier transformation to determine the amplitude or power of the contributing frequencies. Frequencies are classified into very low frequency (VLF: < 0.04 Hz), low frequency (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.4 Hz). Frequency-domain methods are preferred to time-domain methods when investigating short-term recordings.<sup>1</sup> The parameters included for analysis were VLF power, LF power, HF power, total power, and the ratio of LF power to HF power (LF/HF ratio).

We assessed the same HRV parameters as predictors of the following secondary outcomes: ICU stay duration, need for invasive ventilation, inotrope/vasopressor therapy, and renal replacement therapy. We then compared the defined HRV parameters and the APACHE II score as predictors of all study outcomes. Invasive ventilation, inotrope/vasopressor therapy and RRT were defined as the need for the use of any of those modalities during the study period without consideration of their duration of use or dose.

### Statistical analysis

The number of eligible patients admitted during the study period determined the sample size. Baseline characteristics of the included patients were reported as mean (standard deviation [SD]) for continuous variables and count (per cent) for categorical variables. To address the primary endpoint we first determined the proportion of patients who died at 30 days, together with their associated 95% confidence intervals. We then performed univariable logistic regression for each of the candidate predictor variables (VLF power, LF power, HF power, total power, and LF/HF ratio) to determine their association with the primary outcome. We log transformed variables not normally distributed before performing this analysis.

Predictors associated with the primary outcome (i.e.  $p < 0.1$ ) were entered into a multivariable regression model. For all logistic regression analyses we used backward stepwise models. We assessed collinearity using the variance inflation factor (VIF), which measures the extent to which the variance of the model coefficients will be inflated (because of the correlation of the variable with other predictor variables) if that variable is included in the model. We considered variables with VIF > 10 co-linear and we excluded the variable with the lowest odds ratio (OR) on univariate analysis from the model.

For the study outcome of ICU stay we evaluated each of the variables identified as significantly predictive of the primary outcome in the preceding analysis, to determine their association with this secondary outcome. We then conducted linear regression to determine the strength of association. For the study outcomes of need for invasive ventilation, need for inotrope/vasopressor therapy, and need for renal replacement therapy we conducted logistic regression as detailed above to determine the strength of association between the HRV parameters and these outcomes.

We compared HRV variables identified as significantly predictive of the primary outcome with the APACHE II for the prediction of mortality at 30 days after ICU admission.

For all regression models, we reported the OR, corresponding standard error, 95% confidence intervals (CI) and associated  $p$ -values. We reported  $p$ -values to 3 decimal places with  $p$ -values less than 0.001 reported as  $p < 0.001$ . For all tests, we used an alpha = 0.05 level of significance. Examination of residuals provided an assessment of model assumptions for regression analyses. For the logistic regression model goodness-of-fit was performed using the appropriate Hosmer–Lemeshow tests. For the linear regression model performance was evaluated using adjusted  $R^2$  and ANOVA.

### Results

As shown in Figure 1, 92 patients were admitted during the study period, of which 78 were eligible for inclusion on admission criteria. Seven patients were discharged without sufficient time for Holter analysis. One patient was excluded because he was in atrial fibrillation and four patients either did not receive Holter analysis or had a recording of insufficient length. Eleven patients were lost to follow-up and thus the primary outcome could not be determined.

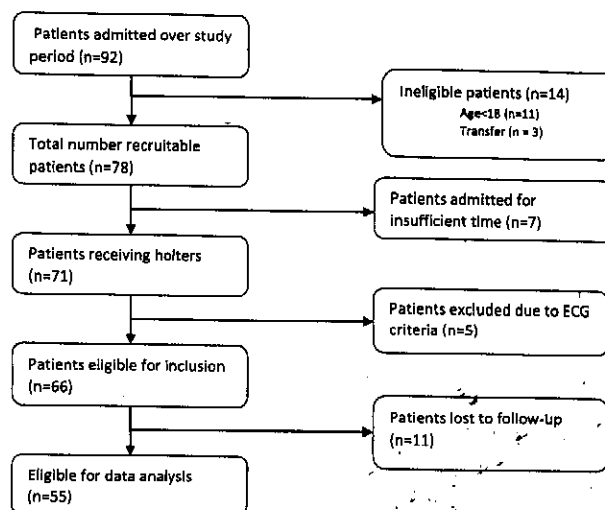


Figure 1: Patient flow chart.

### Population characteristics

There were 55 patients included in the final analysis, 41 from Edendale Hospital ICU and 14 from Grey's Hospital ICU: 22 female and 33 male. Average patient age was 42.3 years (range 20–84) with admissions from a variety of clinical disciplines: trauma (31%), internal medicine (24%), general surgery (22%), obstetrics (9%), urology (7%), orthopaedic surgery (5%) and gynaecology (2%). Thirty-five patients were admitted following surgery (64%). Eighteen of the 55 patients died within 30 days (33%). Thirty patients required invasive ventilation (55%), 19 required inotropic support (35%) and 2 needed renal replacement therapy (4%). The median duration of stay in ICU was 2.6 days (Range 1–22 days).

On univariate analysis, all candidate variables showed an association ( $p > 0.1$ ) with the primary outcome (VLF  $p = 0.002$ , LF  $p = 0.058$ , HF  $p = 0.036$ , TP  $p = 0.002$ , LF/HF  $p = 0.046$ ) and were thus entered into a multivariable regression model. This is shown in Table 1.

Following assessment for collinearity, HF and TP were excluded from further analysis (VIF  $> 10$ ). VLF, LF and LF/HF were entered into the model for backward stepwise logistic regression and VLF was shown to be significant ( $p = 0.016$ ); the quality of model fit was good. These findings showed that VLF predicted 30-day mortality in ICU (OR 0.6; 95% CI 0.396–0.911;  $p = 0.016$ ). HRV parameters were not predictive of any of the secondary outcomes, i.e. the need for ventilation, inotrope usage or duration of ICU stay. There were too few outcomes to perform analysis on RRT.

Having established VLF as the primary predictor of 30-day mortality, we compared VLF with APACHE II. Univariate analysis of APACHE II to 30-day mortality showed a strong association ( $p < 0.001$ ). After log transformation the signal remained strong ( $p < 0.001$ ). We then compared VLF and APACHE II. VLF remained predictive in the presence of the APACHE II score, suggesting that VLF provided additional predictive information above and beyond the APACHE II score.

### Discussion

This study aimed to assess the utility of HRV parameters for the prediction of 30-day mortality after admission to ICU. We targeted frequency domain parameters as these are the recommended method for short-term analyses and this methodology has been used previously in similar clinical situations.<sup>3,8</sup> We found VLF to be predictive of 30-day ICU mortality (OR 0.6; 95% CI 0.396–0.911;  $p = 0.016$ ). This finding confirmed the work by Schmidt *et al.*<sup>8</sup> and Stein *et al.*<sup>9</sup> showing that VLF predicts poor outcome in the ICU setting. Furthermore, when compared with APACHE II, VLF appeared to have independent predictive value, in keeping with Yien *et al.*<sup>10</sup> HRV parameters were not independently predictive for any of the secondary outcomes (i.e. need for ventilation, inotropes or RRT, duration of ICU stay).

We focused on using HRV measures in a practical manner and in a real-world setting. Accordingly we used the lowest recommended duration for ECG recordings for the frequency domain analysis ( $> 5$  minutes), and allowed for a three-hour period during which the ECG recording could be taken. Guidelines for the examination of VLF power reflect caution in using this measure in short-term recordings,<sup>1</sup> possibly because the influences on VLF power (such as hormonal systems) exert their influence over a longer period. Previous studies reporting on VLF power used 25-minute<sup>10</sup> and 24-hour recordings. It is significant that in our study VLF retained its predictive power even with short-term recordings used in a real-world environment. The autonomic contribution to frequency domain parameters is known to be different, with predominantly sympathetic influence over HF, and a balance of sympathetic and parasympathetic input into lower frequency variables.<sup>1</sup> VLF is influenced by a large number of variables, including temperature, hormonal state and a strong parasympathetic influence.<sup>1,6,11</sup> This may explain differing performances with respect to predictive ability over other frequency domain parameters in the intensive care setting.<sup>3</sup>

HRV is increasingly gaining popularity as a predictor of outcome in a variety of clinical environments, including trauma patients,<sup>12</sup> critically ill emergency department<sup>4</sup> patients,<sup>13</sup> septic patients on admission to ED,<sup>14</sup> and the haemodynamically stable trauma patient.<sup>15</sup> It has also been used to predict outcomes such as hypotension during obstetric spinal hypotension.<sup>16,17</sup> Its use in ICU and anaesthesia has been extensively reviewed elsewhere.<sup>7</sup> There has been a significant amount of research into altered HRV in neonates with changes in HRV preceding clinical markers for the diagnosis of sepsis in neonates,<sup>18,19</sup> as well as being predictive of mortality in this group of patients.<sup>20,21</sup> In adult patients, altered HRV has also been shown to be an early marker of the onset of multiple organ dysfunction<sup>4</sup> and has been shown to be predictive of outcome in head injury patients.<sup>22,23</sup> It has been shown that HRV decreases with sedation<sup>24</sup> and increases with sedation interruption.<sup>25</sup> There is also evidence to suggest that depressed HRV is predictive of overall outcome in the critical care unit.<sup>26</sup> Risk stratification in the ICU and the role of the various components of HRV analysis has also been further delineated in some detail.<sup>2</sup> A study by Yien *et al.*, which looked specifically at HRV criteria to predict outcome in the ICU, showed that increases in the power density values of the LF and VLF components of HRV were related to improved outcome, while a decrease in these components was related to worse outcome.<sup>10</sup> There was a positive correlation with APACHE II scores. The recordings in this study were taken from heart rate signals over 25 minutes and using an algorithm designed in the unit that was being studied.

In our study we found HRV to provide additional predictive information to the APACHE II scores. General illness severity scores are widely used in the ICU to assess resource use, predict

Table 1: Univariable logistic regression analysis of log-transformed candidate variables

Variable	Odds ratio	Standard error	p-value	Confidence interval
VLF	0.571	0.104	0.002*	0.399–0.816
LF	0.678	0.139	0.058*	0.453–1.014
HF	0.687	0.123	0.036*	0.483–0.976
TP	0.579	0.102	0.002*	0.409–0.818
LF/HF	0.691	0.128	0.046*	0.480–0.994

Results reported to three decimal places. (VLF: very low frequency; LF: low frequency; HF: high frequency; TP: total power; LF/HF: low frequency:high frequency ratio).

\*p-value  $< 0.1$  for entry into multivariable regression model.

outcome, and characterise disease severity and degree of organ dysfunction.<sup>26</sup> APACHE is one of the generic scoring systems, which was revised to APACHE II in 1985 and is designed to predict outcome based on the severity of disease on admission.<sup>27</sup> It is currently the world's most widely used scoring system.<sup>26</sup> APACHE II does not incorporate an HRV component; our study suggests that this could be a consideration.

There are a few limitations to our study. Our investigation occurred as a sub-study of a multi-centre observational outcomes study in ICUs, which limited the total number of patients we could recruit. Our results would have been more robust with a larger cohort. Eleven patients were also lost to follow-up in the parent study and were thus excluded. This affected the study size and introduced the possibility of bias, as these patients were likely to represent patients who survived to hospital discharge. We did not control for a variety of factors that may affect autonomic function, such as feeding status, degree of sedation, type of medication and underlying pathology, as we do not believe it feasible to control for these in a real-world setting. A detailed discussion on confounders and their effects in HRV studies in ICU has been published elsewhere.<sup>67</sup> The use of APACHE II in a general ICU is also problematic because the original developmental data-set for APACHE II did not include trauma and obstetrics subsets. However, both ICUs in our study collect APACHE II scores as part of routine clinical governance and this information was also being collected as part of the 30DOS study. Subset analysis was not performed as the small sample size would lead to an over-fitted model. Our results still reflect that HRV adds value to what remains the most widely used scoring system worldwide.

HRV appears to hold promise as a predictor of outcome, despite numerous challenges with HRV research in the ICU.<sup>28</sup> Currently it is difficult to incorporate measurements into routine clinical care without modification and streamlining of the collection methods. Technically this should be easy to do by adding software to conventional monitors used in the ICU setting, the majority of which have an ECG sampling frequency sufficient to meet the standards set in guidelines for the use of HRV analysis.<sup>1</sup> Current guidelines are now dated,<sup>1,28</sup> and additional pragmatic research is required to further define which parameters are worth investigating. This study found that VLF independently predicted all-cause mortality at 30 days after ICU admission. VLF provided additional predictive ability above that of the APACHE II score. As suggested by this exploratory analysis larger multi-centre studies seem warranted.

**Disclosures** – No author has any conflict of interest.

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