



## Article

# Heart rate variability: Measurement and emerging use in critical care medicine

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## Heart rate variability: measurement and emerging use in critical care medicine

### Introduction

Stephen Hales in 1733 was the first to report that the time interval between individual arterial pulsations varied in horses.<sup>1</sup> Since then, the introduction of ambulatory ECG has led to the recognition that the time period between successive R waves on the ECG varies in mammals.<sup>1, 2</sup> This variability between heartbeats or R-R interval (RRi) is a feature of the healthy cardiovascular system and is more commonly known as the heart rate variability (HRV).<sup>2,3</sup>

Hon and Lee first recognised the clinical potential of HRV when they noted that acute alterations in the HRV were a marker of foetal distress and predicted foetal hypoxia.<sup>4</sup> Today, monitoring the variability of foetal heart rate has become a standard of care and has been responsible for significant reductions in foetal morbidity and mortality.<sup>5,4</sup> Similar alterations in HRV have been recognised post myocardial infarction and are associated with a 5-fold increase in mortality.<sup>6,7</sup> More recently, reduced HRV parameters have been reported as an independent predictor of 30-day mortality and provided additional predictive value over APACHE II scores in critically unwell patients.<sup>8</sup>

The increased appreciation of the clinical potential of HRV analysis has led to its use in various clinical situations common to intensive care medicine including multiorgan dysfunction syndrome (MODS), sepsis and trauma.<sup>9,10,11</sup> With this in mind, the following review aims to discuss the physiological basis of HRV, the measurement of HRV and the emerging clinical role of HRV analysis in intensive care medicine.

### Physiological basis of HRV

Automaticity is common to cardiac pacemaker tissue however, heart rate and rhythm is continuously altered and regulated by the autonomic nervous system (ANS).<sup>12,2</sup>

The parasympathetic nervous system (PNS) innervates the sinoatrial node, the atrioventricular node, and the atrial myocardium via the vagus nerve.<sup>13,1</sup> Parasympathetic activation leads to release of acetylcholine (ACh) which slows the heart rate and lengthens the R-R interval.<sup>1,13</sup> Parasympathetic activation leads to an almost immediate reduction in heart rate due to the very short latency of effect of ACh and the rate at which ACh is rapidly metabolised and cleared.<sup>1,2</sup> Therefore the PNS regulates heart rate on a near beat by beat basis.<sup>1</sup> In contrast, sympathetic nervous system (SNS) activation initiates the synaptic release of catecholamines, that increase cardiac contractility and heart rate.<sup>1,2</sup> The action of catecholamines is slow compared to that of ACh and results in a delay between the onset of sympathetic stimulation and changes in heart rate of approximately 5 seconds.<sup>1,14</sup> Despite the slower onset, sympathetic stimulation has a longer duration of action; affecting heart rate for 5-10 seconds following the cessation of a sympathetic stimulus.<sup>1,14</sup> The differences in neurotransmitters between the PNS and SNS has led to the recognition that the effects of each arm of the ANS are not opposite and symmetrical but confer overlapping and different time frequencies of action.<sup>1</sup>

90 In healthy individuals' cyclical changes in HRV occur with respiration and fluctuations in  
91 blood pressure.<sup>15,16</sup> Frequency domain and power spectral density (PSD) analysis utilizes  
92 fast Fourier transform (FFT) analysis to describe oscillations in the RRi and transform them  
93 into discrete frequencies that help to conceptualise our understanding of the physiological  
94 mechanisms responsible for HRV.<sup>17,18</sup>

95

96 Since cyclical changes in HRV are associated with respiration and occur at a high frequency  
97 (HF) of 0.25Hz they are thought to dominate a number of cardiorespiratory and neural  
98 interactions.<sup>16,2</sup> These interactions are responsible for the observation of respiratory sinus  
99 arrhythmia (RSA), characterised by shortening of the RRi with inspiration and lengthening  
100 with expiration.<sup>1</sup> Abolition of these high frequency oscillations can be achieved by  
101 parasympathetic blockade with atropine suggesting that they are parasympathetically  
102 mediated.<sup>15</sup>

103

104 Cyclical changes associated with fluctuations in arterial blood pressure (ABP) occur at a low  
105 frequency (LF) of 0.10Hz and are thought to be mediated by the SNS.<sup>2</sup> These oscillations  
106 occur in synchrony with arterial Mayer waves.<sup>1</sup> Mayer waves are spontaneous oscillations in  
107 ABP whose amplitude is thought to measure sympathetic vasomotor tone.<sup>16</sup> Mayer wave  
108 oscillations are thought to parallel oscillations in HRV and in particular the LF oscillations  
109 recognised in HRV.<sup>1</sup> These are attenuated and completely abolished by alpha adrenergic  
110 antagonist drugs suggesting that sympathetic activity is important in the generation of these  
111 oscillations.<sup>1</sup> There remains debate as to the precise physiological origin of Mayer waves in  
112 the generation of heart rate frequencies at 0.10Hz and controversy exists in attributing all LF  
113 HRV oscillations to sympathetic modulation.<sup>19</sup> Research has demonstrated that  
114 parasympathetic blockade also produces modulation of low frequency oscillations in HRV.<sup>1</sup>  
115 Despite this, measurement of HF and LF oscillations calculated as a ratio of LF/HF has been  
116 suggested as a measure of sympathovagal balance with relative changes in the magnitude  
117 of each frequency reflecting the dominance of a particular arm of the ANS.<sup>2,15</sup>

118

119 HF and LF components of HRV account for only 5% of the total power of HRV recordings  
120 measured by power spectral density analysis. The remaining 95% is accounted for by two  
121 other frequencies called the very-low frequency (VLF) band and ultra-low frequency (ULF)  
122 band.<sup>13</sup> Historically these frequency components have not been well characterised.  
123 However, recent research suggests that the VLF band is associated with thermoregulatory  
124 mechanisms, changes in peripheral chemoreceptor activity and fluctuations in the renin-  
125 angiotensin system (RAAS) whilst the ULF band is thought to reflect oscillations due to  
126 circadian rhythm.<sup>20,17</sup> Despite relatively less being known about the VLF and ULF  
127 frequencies, they appear to be clinically important as reduced variability in the VLF band is  
128 associated with arrhythmias, high inflammation levels and increased mortality.<sup>21</sup>

129

### 130 **Measuring Heart Rate Variability**

131

132 In 1996 The European Society of Cardiology and the North American Society of Pacing and  
133 Electrophysiology published guidelines aimed at standardising the terminology and  
134 methodology used in the measurement of HRV.<sup>12</sup> These guidelines describe a number of  
135 methods for measuring HRV including linear measures such as time domain and frequency  
136 domain measures and non-linear measures such as the Poincare plot.<sup>12</sup> Recent advances in

137 biological systems theory, HRV analysis and complexity analysis have resulted in updated  
138 guidance for non-linear techniques such as entropy and fractal analysis that focus on  
139 similarities in the RRi over a given time period.<sup>20,22</sup>

140

#### 141 **Time domain measures**

142

143 Time domain measures derive HRV using either statistical or geometric analysis.<sup>12</sup> Statistical  
144 analyses (e.g. standard deviation) are applied to the RRi to measure variation over a  
145 specified period of time from <1min to 24 hours.<sup>12, 20</sup> Geometric derivation of HRV requires  
146 that a series of RRi are converted into a geometric pattern, such as a sample density  
147 distribution of RRi and analysed using statistical methods (Table 1).<sup>12,23</sup>

148

149 Time domain measures are easy to calculate and simple to derive.<sup>12,24</sup> However, they are  
150 sensitive to artefact particularly **supraventricular and ventricular extrasystolic** beats.<sup>24</sup>  
151 Therefore, ECG recordings need careful pre-processing to ensure removal of **extrasystolic**  
152 **beats** and interference. Similarly, they require stationarity in the time series (i.e. the mean  
153 heart rate does not change significantly), which is a property not often met in biological  
154 systems.<sup>24</sup> For these reasons time domain measures cannot discriminate between  
155 alterations in SNS or PNS output. Despite this, they can be used to assess overall ANS  
156 activity, and provide useful clinical information.<sup>1,24</sup>

157

#### 158 **Frequency domain measures**

159

160 Frequency domain measures describe variation in the RRi following transformation into  
161 different frequency components. Frequency domain measures are derived using FFT  
162 analysis to provide information on the frequency components of HRV over a time series  
163 (Figure 1).<sup>2,12,24</sup> In analysis of 2 to 5 minute ECG recordings three characteristic frequencies  
164 are recognised, LF, HF and VLF (Table 1).<sup>24</sup> In 24 hour recordings the ULF band is recognised  
165 with the VLF band.<sup>12</sup> In general, to accurately determine the power of a LF banding a  
166 recording greater or equal to approximately 5/f is required. Frequency domain, like time  
167 domain analysis, is sensitive to artefact, ectopic beats and require stationarity in the data  
168 series.<sup>24</sup> Physiological mechanisms such as changes in posture, levels of stress and  
169 movement are thought to alter LF and HF readings, therefore, factors that are known to  
170 modulate the ANS should be controlled during HRV measurement.<sup>12, 24, 25</sup>

171

#### 172 **Non-linear measures of HRV**

173

174 Non-linear measures overcome the requirement of stationarity in data unlike the linear  
175 measures.<sup>20,26</sup> They include techniques such as the Poincare plot, detrended fluctuation  
176 analysis (DFA) and approximate and sample entropy analysis (ApEN and SampEN).<sup>26</sup> Non-  
177 linear measures model dynamic systems using variables that cannot be plotted on a straight  
178 line.<sup>22</sup> Physiological systems are dynamic due to complex interactions between  
179 cardiovascular, endocrine and autonomic systems and do not ordinarily display stationarity.  
180 Therefore non-linear measures may offer a number of advantages over linear HRV measures  
181 when stationarity cannot be guaranteed.<sup>26</sup> The non-linear methods implicitly assume that  
182 the factors that create HRV occur as oscillatory inputs with associated random variation.<sup>27</sup>  
183 Non-linear methods borrow techniques from fractal mathematics and produce variables

184 that describe the pattern of variability by analysing temporal similarities in the signals.<sup>27</sup>  
185 Typically, parameters are derived that separately describe the scaling of short-term  
186 variability (e.g. <10 beats) and longer-term trends. Whilst, as yet, these parameters do not  
187 offer a great deal of mechanistic insight, they are robust and can distinguish between  
188 patient groups.<sup>2</sup>

189

### 190 ***Poincare plot***

191

192 Poincare plots are a graphical representation (scatter plot) of HRV generated by plotting  
193 each RRi against the prior RRi (Figure 2).<sup>20</sup>

194

195 Poincare plots are analysed by fitting an ellipse to the data series. Three non-linear  
196 measures are typically derived, SD, SD1 and SD2 (Table 1).<sup>20</sup> Total variability (S) in the  
197 sample is represented by the entire area of the ellipse.<sup>20</sup>

198

### 199 ***Detrended fluctuation analysis***

200

201 DFA correlates the fluctuations between RRi over different time scales and analyses  
202 temporal self-similarities in the RRi.<sup>27</sup> Short term fluctuations are represented by DFA $\alpha$ 1  
203 whilst long-term fluctuations are represented by DFA $\alpha$ 2.<sup>20</sup> The calculation of DFA involves  
204 several steps and during the calculation, non-stationarity in the signal is addressed by  
205 subtraction of extrinsic fluctuations, this has been extensively reviewed elsewhere.<sup>28</sup> The  
206 primary advantage of DFA is removal of confounding due to non-stationarity during DFA  
207 calculation.<sup>29</sup> However it requires large data sets and whether it offers further information  
208 compared to other techniques requires further investigation.<sup>28,24</sup>

209

### 210 ***Entropy***

211

212 Entropy analysis can be applied to a series of RRi and provides a measure of the degree of  
213 irregularity or “randomness” within the series<sup>24</sup>. The technique essentially calculates the  
214 probability that any given sequence of intervals within the RRi series will be repeated.<sup>27</sup> The  
215 more likely to be repeated the lower the calculated entropy. Measures of such entropy  
216 include the ApnEN and SampEN respectively. Clinically, lower entropy values correlate to a  
217 state of illness<sup>24,30</sup>. SampEN was introduced to address the sensitivity of ApnEN to sample  
218 size and the inaccuracy of ApnEN when the number of data points are low in a time series<sup>24</sup>.

219

### 220 **Factors affecting HRV measurement**

221

222 Despite the promising ability of HRV to provide information on biological systems there  
223 remains a number of physiological and technical issues that need to be considered when  
224 interpreting HRV clinically. The context of HRV recording is crucial, as numerous factors  
225 including age (increased age leads to reduced HRV), gender (higher HRV in females), resting  
226 heart rate and recent physical activity, are thought to alter HRV.<sup>20</sup> Factors such as posture  
227 and movement also need to be considered as it has been shown that HRV is markedly  
228 altered between standing and supine positioning.<sup>12</sup> HRV is also affected by a number of  
229 technical factors such as ECG sampling frequency, length of ECG recording and the presence  
230 of artefact or interference.<sup>12,20</sup> To detect the R wave fiducial point on the ECG a sampling

231 frequency minimum of 500Hz is recommended.<sup>12</sup> However as HRV decreases with illness it  
232 may be necessary to sample at a much higher frequency to ensure adequate resolution and  
233 accuracy.<sup>20</sup> A recent systematic review of HRV use in critical care highlighted that a  
234 significant number of studies used sampling frequencies as low as 250Hz and these results  
235 should be considered with caution.<sup>11</sup> Similarly, the length of recording is crucial and can  
236 significantly affect time and frequency domain HRV measures. Recommendations have been  
237 made regarding acceptable ECG recording lengths for each HRV measure, however the  
238 existing literature often fails to accurately report the duration of ECG recordings used in  
239 studies, potentially introducing an element of uncertainty to their results.<sup>11,12</sup> Artefacts can  
240 significantly distort time and frequency domain HRV measures and the bias of a single  
241 artefact can distort the entire HRV recording. Manual inspection of ECG is recommended to  
242 ensure HRV analysis is conducted on ECG segments that are free of artefact, ectopic beats,  
243 missed beats and interference.<sup>12</sup> Artefacts such as missed and ectopic beats can be resolved  
244 by artefact removal and interpolation of an R wave based on previous QRS intervals.<sup>20</sup>  
245 However, with increasing interpolation of R waves a significant amount of noise to signal  
246 ratio can be introduced in the data series and lead to errors in HRV measures. **Similarly,**  
247 **arrhythmias such as atrial fibrillation (AF) can introduce significant distortion in HRV and**  
248 **therefore should not be considered accurate in patients with AF.** These factors need to be  
249 considered when interpreting HRV in the clinical context.

250

251

## 252 **HRV in Intensive Care Medicine**

253

254 **HRV is frequently used to describe the activity of the SNS and PNS. However, this relies on**  
255 **the assumption that the autonomic nervous system is in balance, with low PNS activity**  
256 **associated with a correspondingly high SNS activity and vice versa.<sup>31</sup> Many authors have**  
257 **refuted this, and it is generally accepted that the relative balance of the ANS is more**  
258 **complex.**

259

260 **Similarly, mechanisms responsible for RRI and HRV are complex and reflect inputs from**  
261 **multiple physiological systems, including the SNS, PNS, renin-angiotensin system,**  
262 **thermoregulatory systems, as well as mechanical inputs from respiration and alterations in**  
263 **arterial blood pressure.<sup>32</sup>**

264

265 **Despite debate regarding the association between HRV and the ANS, the previous two**  
266 **decades have witnessed a significant expansion in the use of HRV analysis and increasing**  
267 **evidence supporting its use in critical care.<sup>11</sup>**

268

269 Autonomic dysfunction is common to a number of disorders seen in critical care patients,  
270 such as MODS, sepsis, myocardial infarction, decompensated heart failure and severe brain  
271 injury (SBI).<sup>11,33,34</sup> The ability to assess autonomic function may provide valuable  
272 information regarding the pathophysiology, severity and prognosis of these disorders.<sup>33</sup>  
273 **However the reader is reminded that whilst an association between HRV and the ANS**  
274 **certainly exists, HRV does not directly measure autonomic activity and any association is**  
275 **likely a combination of complex physiological inputs.<sup>31</sup> With this in mind the remainder of**  
276 **this review will focus on areas in which HRV has found utility in intensive care medicine.**

277

## 278 **Multiple organ dysfunction syndrome and Sepsis**

279

280 As early as 1995 it was recognised that SDNN, LF, LF/HF are reduced in sepsis.<sup>11,35, 36,37</sup> Godin  
281 and Buchman suggested that organ systems are connected to each other via neural,  
282 hormonal and cytokine networks and that they each behave as biological oscillators.<sup>38</sup> They  
283 hypothesised that sepsis resulted in an uncoupling of organ systems and leads to a  
284 reduction in HRV parameters.<sup>38,30</sup> They proposed that HRV was a method for the  
285 quantification of 'inter-organ communication' and yielded valuable information in the  
286 pathophysiology of sepsis and prognosis of patients admitted to the intensive care unit  
287 (ITU).<sup>38</sup> Recently, Bishop et al reported that reduction in the VLF domain was predictive of  
288 30 day all-cause mortality in patients admitted to ITU.<sup>39</sup> Similar findings have been reported  
289 by Schmidt who found that a reduced VLF was predictive of 28 day mortality in patients with  
290 MODS.<sup>40</sup> HRV analysis may be able to predict mortality early in a patient's presentation,  
291 with Chen reporting that a reduced SDNN was predictive of in-hospital mortality in septic  
292 patients admitted to the accident and emergency department.<sup>9</sup> Interestingly, Chen also  
293 reported that an increased HF was predictive of hospital survival, suggesting that health is  
294 associated with a high degree of variability.<sup>9</sup> This was confirmed by Papaioannou in a novel  
295 study that tracked changing HRV in response to a patient's pathophysiological state.<sup>41</sup> SOFA  
296 scores were longitudinally tracked with a number of HRV measures over time and revealed  
297 that entropy was reduced in non-survivors, and the long term non-linear HRV parameter  
298 DFA $\alpha$ 2 correlated with length of ITU stay.<sup>41</sup> Moreover, patients that were more clinically  
299 unstable had a reduced LF/HF ratio, and a reduction in overall variance.<sup>41</sup> This recovered as  
300 patients improved and were finally discharged from critically care, suggesting that HRV  
301 analysis may be valuable as a method of monitoring physiological deterioration and offer  
302 real time prognostication in critically unwell patients.<sup>41</sup>

303

304 HRV may also serve to predict those patients at risk of deterioration and those who may  
305 benefit from early ITU admission. In a recent observational study in septic emergency  
306 department patients, Samsudin et al report a scoring system utilising two vital signs  
307 (respiratory rate and systolic blood pressure), age and two HRV measures (mean RRi and  
308 DFA $\alpha$ 2).<sup>42</sup> They revealed that the use of HRV not only outperformed SOFA, NEWS and  
309 MEWS scoring at prediction of 30 day mortality but, was also able to accurately predict  
310 those patients requiring ITU admission and intubation.<sup>42</sup> Similar scoring systems utilising  
311 HRV have already shown promise in neonatal patients. In the landmark HeRO Trial,  
312 Moorman et al revealed that monitoring heart rate characteristics including reduced  
313 variability and transient heart rate decelerations, led to a 22% relative reduction in mortality  
314 in very low birthweight neonates.<sup>43</sup> The HeRO trial provided clinicians with a score based  
315 upon a composite measure utilising SD RRi, sample asymmetry (a measure of transient  
316 accelerations and deceleration of the heart rate) and SampEN.<sup>44</sup> Using multivariable logistic  
317 regression and mathematical algorithms, the HeRO score provides continuous non-invasive  
318 monitoring that estimates the fold-increase in the probability of sepsis.<sup>44,43</sup> The HeRO trial  
319 and scoring systems developed by Samsudin hint at the possibility of a new generation of  
320 physiometers for the earlier detection of deterioration and sepsis.<sup>42,44</sup>

321

## 322 **HRV and inflammation**

323



324 Inflammation is associated with a number of conditions that present to ITU such as  
325 myocardial infarction, sepsis, systemic inflammatory response syndrome, MODs and severe  
326 trauma.<sup>45</sup> Factors that trigger inflammation also enhance anti-inflammatory pathways that  
327 counterbalance the initial pro-inflammatory signal.<sup>45, 21</sup> An inflammatory reflex has been  
328 described in which cytokines induce neuroendocrine modulatory mechanisms that signal via  
329 the autonomic nervous system.<sup>21,45</sup> In response to inflammation vagal outflow increased  
330 systemically and more specifically to organs such as the spleen that are thought to be  
331 responsible for the upregulation of anti-inflammatory cytokine levels.<sup>45,46</sup> It is thought that  
332 this counter-regulatory mechanism confers protection against unregulated tissue damage in  
333 inflammatory conditions and poly-microbial infection and is known as the 'cholinergic anti-  
334 inflammatory pathway.'<sup>45</sup> HRV analysis has helped elucidate the role the ANS plays in the  
335 inflammatory reflex, and a depressed parasympathetic activity has been implicated in the  
336 pathogenesis of diseases associated with an exaggerated inflammatory response.<sup>45</sup> A  
337 number of authors have correlated HRV with inflammatory markers.<sup>21,47,48</sup> Tateishi  
338 investigated the relationship between IL-6 and HRV in patients admitted to critical care with  
339 sepsis and found that IL-6 was negatively correlated with the LF component of HRV  
340 analysis.<sup>47</sup> Papaioannou tracked patients from admission to critical care and reported an  
341 inverse correlation between LF and LF/HF and C-reactive protein (CRP) levels.<sup>21</sup> HF HRV was  
342 correlated with IL-10 levels, suggesting that LF/HF ratio and reduced LF HRV is related to  
343 both pro-inflammatory and anti-inflammatory responses.<sup>21</sup> Furthermore, those patients  
344 that developed shock had increased biomarkers (CRP, IL-6, IL-10) and decreased HRV,  
345 reaching statistical significance in patients with a SOFA score >10.<sup>21</sup> This suggests that HRV is  
346 related to both anti-inflammatory and pro-inflammatory signals with a stronger association  
347 being present in patients that are more unwell.<sup>21</sup>

348

349 There is strong evidence that the ANS influences the physiological response to inflammation  
350 and recent research suggests that the anticholinergic anti-inflammatory pathway may hold  
351 promise as a therapeutic target.<sup>21,49</sup> HRV measurement may therefore prove to be a novel  
352 physiomaer that characterises the cardiorespiratory responses to inflammation and may  
353 have prognostic value in any future anti-inflammatory treatments.<sup>50</sup>

354

### 355 **Cardiovascular disorders, arrhythmias and cardiac arrest**

356

357 It is generally accepted that HRV is a powerful predictor of cardiac mortality, arrhythmia and  
358 sudden cardiac death, and is independent of other risk factors (left ventricular ejection  
359 fraction, ventricular extra-systoles and episodes of non-sustained ventricular tachycardia)  
360 after myocardial infarction.<sup>5,7,12,51</sup> A substudy of the large ATRAMI trial found that  
361 decreased SDNN and impaired heart rate response to an increase in blood pressure  
362 (baroreceptor sensitivity) were predictors of cardiac mortality.<sup>52</sup> In patients with a reduced  
363 ejection fraction, the presence of a reduced SDNN or low baroreceptor sensitivity carried a  
364 relative risk of mortality of 6.7 and 8.7 respectively.<sup>52</sup> Reduced HRV may also provide an  
365 early warning of deterioration as Passariello et al has shown that patients who suffer  
366 sudden cardiac death secondary to fatal arrhythmia have a marked decrease in SDNN in the  
367 five minutes preceding its onset.<sup>53</sup> Similar findings are reported in patients that suffer from  
368 paroxysmal AF, where ApnEN was decreased up to 100 minutes prior to the onset of  
369 arrhythmia.<sup>22</sup> That HRV analysis appears to be able to predict patients at risk of cardiac

370 mortality and arrhythmias may prove useful for risk stratification, particularly in patients at  
371 increased cardiovascular risk such as in the peri-operative period.<sup>33</sup>

372

373 HRV has also been used to monitor the responses to drug treatment in patients with  
374 cardiovascular disease and hypertension. Beta-antagonists such as metoprolol and atenolol  
375 tend to augment HF whilst reducing LF in patients with hypertension.<sup>54</sup> Similar findings have  
376 been reported post myocardial infarction, where the addition of metoprolol led to a  
377 reduction in LF output.<sup>54</sup> However, cardiovascular drugs such as, statins and calcium channel  
378 antagonists have been found to have a variable effect on HRV.<sup>11</sup> Interestingly drugs that  
379 would be expected to have profound effects on the ANS such as catecholamines have also  
380 been shown to have variable effects on HRV. A recent systematic review reported three  
381 studies that did not show any association between HRV parameters and vasopressor  
382 requirement or administration of exogenous catecholamines.<sup>11</sup> Despite no finding of an  
383 association the authors highlighted that the majority of studies failed to report the  
384 administration of cardiovascular drugs, vasopressors or catecholamines and had limited  
385 ability to draw any conclusions regarding the potential effects on HRV.<sup>11,54</sup>

386

387 HRV may also offer important information regarding neurological recovery post cardiac  
388 arrest.<sup>33,55</sup> Tiainen et al in a randomised trial reported significantly higher HRV measures in  
389 those patients that underwent therapeutic hypothermia (TH) compared to normothermia  
390 post cardiac arrest.<sup>55</sup> Higher SDNN, SDANN, HF and LF measures were recorded in the first  
391 48 hours of TH.<sup>55</sup> The authors suggest that higher HRV measures may represent a beneficial  
392 effect on myocardial function and preservation of ANS function or the neuroprotective  
393 effects of cooling.<sup>55</sup> However, they acknowledge that this finding may be due to  
394 confounding and secondary to the relative bradycardia that TH induces in patients.<sup>55</sup> The  
395 exact mechanism underlying improved HRV with TH remains uncertain, despite this the  
396 potential of HRV to predict outcome post cardiac arrest should be confirmed with larger  
397 trials.<sup>33,55</sup>

398

### 399 **Neurological disorders**

400

401 Lowhenshon was amongst the first authors to investigate the links between HRV and  
402 neurological disorders.<sup>56</sup> In brain-damaged adults Lowhenshon revealed that HRV decreased  
403 and rapidly diminished in line with increases in intracranial pressure (ICP).<sup>56</sup> A more recent  
404 study in 145 trauma patients confirmed that an increase in intracranial pressure, as  
405 measured by invasive intracranial pressure monitoring, is preceded by a reduction in heart  
406 rate variability.<sup>57</sup> Reduction in HRV has been shown to be proportional to the increase in  
407 intracranial pressure, with more marked alterations in HRV occurring when ICP was  
408 >30mmHg or cerebral perfusion pressure <40mmHg.<sup>33</sup> Moreover, reductions in HRV  
409 preceded changes in ICP by approximately 24 hours.<sup>57</sup> These findings suggest that HRV may  
410 function as a non-invasive method of monitoring early changes in intracranial pressure and  
411 may identify those patients that would benefit from invasive monitoring.<sup>57</sup>

412

413 Complications following subarachnoid haemorrhage (SAH) can include severe vasospasm,  
414 neurogenic stress cardiomyopathy, and cardiac arrhythmias.<sup>58</sup> Reduction in RMSSD has  
415 been shown to be associated with neurogenic stress cardiomyopathy following SAH.<sup>58</sup>  
416 Similar alterations in HRV have been recognised in extradural, subdural, and intracerebral

417 haematomas.<sup>33</sup> Schmidt et al have investigated VLF reductions and delayed cerebral  
418 ischaemia secondary to cerebral vasospasm in SAH patients.<sup>59</sup> It is thought that VLF may  
419 partly represent parasympathetic outflow and reductions in VLF are associated with states  
420 of high inflammation.<sup>20</sup> Both RMSSD and VLF have been shown to predict complications  
421 following SAH, and it has been suggested that this may be related to the pro-inflammatory  
422 response contributing to the development of cerebral ischaemia after SAH.<sup>59</sup>

423  
424 Changes in HRV have also been shown to be an early indication of the occurrence of brain  
425 death.<sup>60</sup> Conci reported a reduction in the total power of frequency domain analysis and  
426 suggested that these changes likely mirror a cessation of the activity of cardiorespiratory  
427 brainstem centres.<sup>60</sup> These findings have been confirmed by others who measured  
428 continuous HRV and found that the loss of spectral power occurred during the transition to  
429 brain death.<sup>61</sup> Taken together these findings may be useful as a complementary method in  
430 the diagnosis of brain stem death and help inform when more formal brain stem death  
431 testing should occur.<sup>60,61</sup>

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433

## 434 **Conclusion**

435

436 HRV analysis offers a unique monitoring modality that provides information regarding  
437 variability in complex biological signals. Unlike existing monitoring, HRV can potentially  
438 detect and track the state of the whole physiological system over time and during the  
439 development of illness, potentially even before it is clinically apparent. Goldberger  
440 described illness as the de-complexification of complex biological systems and suggested  
441 that health is characterised by 'organised variability' whilst reduced variability is associated  
442 with disease states, such as multi-organ dysfunction syndrome and sepsis.<sup>62</sup> The inclusion of  
443 HRV measures into current early warning scoring systems such as NEWS could potentially  
444 lead to a new generation of physiomarkers that can predict deterioration earlier and help  
445 target those patients at greatest risk of mortality.<sup>42</sup> The HeRO trial and HeRO monitoring  
446 system has shown that incorporation of HRV measures can potentially lead to earlier  
447 investigation and treatment and significantly improved clinical outcomes.<sup>44</sup>

448

449 **Despite the potential of HRV measurement, it is still largely a research technique and has**  
450 **not become part of routine monitoring in critical care.<sup>63</sup> There are a number of potential**  
451 **reasons for this. First, despite the large number of experimental studies, the majority are**  
452 **cohort or case-control studies of low methodological quality.<sup>11</sup> Many studies also failed to**  
453 **fully account for confounding factors such as commonly used drugs in ITU including anti-**  
454 **arrhythmic medications and the impact that interventions in ITU such as mechanical**  
455 **ventilation have on HRV parameters.<sup>11</sup> Second, there is a lack of standardised methodology**  
456 **for the recording, processing and derivation of HRV from ECG. Despite guidelines from The**  
457 **European Society of Cardiology and the North American Society of Pacing and**  
458 **Electrophysiology, obtaining clinically useful HRV parameters still requires clinicians to pre-**  
459 **process ECG and RRi data using standard ECG monitoring equipment before using**  
460 **standalone software to derive HRV parameters.<sup>12</sup> A number of open source software**  
461 **packages written in Matlab mathematical language are available as well as a number of paid**  
462 **software packages such as Kubios and ARTiiFACT.<sup>64,65,66</sup> To date the authors are not aware**  
463 **of any monitoring systems that derive HRV in real-time at the bedside and this likely limits**

464 its widespread use in ITU. Third, despite evidence to suggest that HRV can predict  
465 deterioration, arrhythmias and MODS, the exact pathophysiological mechanisms underlying  
466 these associations remains unclear. Throughout this review we have discussed HRV as a  
467 measure of autonomic function. In reality individual HRV parameters are more complex and  
468 multiple physiological factors impact upon them.<sup>31</sup> Until the exact mechanisms responsible  
469 for measured HRV parameters are uncovered it is difficult to fully define a mechanistic basis  
470 for HRV.<sup>31</sup>

471

472 Measurement of HRV, along with advances in biomedical engineering and computational  
473 methods, has increased our understanding of the role the ANS plays in the pathophysiology  
474 of disease and illness. But for HRV analysis to become a standard of monitoring in critical  
475 care, prospective studies are needed to address the technical considerations, determine  
476 what factors confound HRV analysis, and develop consensus standards for HRV monitoring  
477 in critical care. In conclusion if these challenges are addressed, HRV analysis has the  
478 potential to revolutionise critical care monitoring and introduce an era of monitoring based  
479 upon individualised variability analysis.

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