Supplementary Material for:

"Ectopic Beats, Activity Effects and Heart Rate Turbulence",

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Activity related HRV

Bernardi *et al.* [35] demonstrated that there is a significant range of HRV for different controlled mental activities (see table 1), even when physical activity is controlled for. In particular, these rages are larger the differences in HRV quoted for populations with differing conditions [12,13]. However, it is extremely difficult to control for mental activity (as a subject's thoughts can easily drift). During sleep, mental activity levels can be passively measured and distinct differences in HRV are observed [12,13,20,40,42,43] (see table 2).

Table 1 : LF/HF -ratios during Wakefulness. Taken from Bernardi *et al.* [35].

Activity :	**LF/HF ratio :**
Spontaneous Breathing	**1.39 ± 0.28**
Controlled Breathing (15 rpm)	**0.69 ± 0.37**
Controlled Breathing (18 rpm)	**1.09 ± 0.36**
Silent Reading	**1.52 ± 0.26**
Reading Aloud	**1.59 ± 0.21**
Free Talking	**3.58 ± 0.45**
Performing mentally stressful tasks silently (e.g. arithmetic)	**3.05 ± 0.39**
Performing mentally stressful tasks aloud	**2.89 ± 0.31**

Table 2 : LF/HF -ratios during Wakefulness, NREM and REM sleep. N/A = not available, Post-MI = a few days after myocardial infarction, CNS = non-cardiac related problem. Results quoted from [24,40,42,43].

Activity → Condition ↓	Awake	REM Sleep	NREM Sleep
Normal [42]	N/A	2→2.5	0.5→1
Normal [24]	3.9	2.7	1.7
Normal [43]	4.0 ± 1.4	3.1 ± 0.7	1.2 ± 0.4
CNS Problem [40]	N/A	3.5→5.5	2→3.5
Post-MI [43]	2.4 ± 0.7	8.9 ± 1.6	5.1 ± 1.4

Heart Rate Turbulence

The changes in quasi-stationarity of the sinus rhythm due to bi-phasic physiological change in sinus node activity from PVCs is known as Heart Rate Turbulence (HRT). In HRV analysis, this disturbance is removed from the RR tachogram, assuming that the phase of the RR tachogram is unchanged when the signal returns to the `undisturbed value'. In HRT, the changes in the `disturbed' section are analyzed to extract metrics to quantify the changes. In general, HRT manifests as a short initial acceleration of the heart rate for a few beats, followed by a deceleration back to the basal value from before the PVC. HRT is usually quantified by two numerical parameters; Turbulence Onset (TO) and the Turbulence Slope (TS). TO is defined as the percentage difference between the average value of the first two normal RR intervals following the PVC (RR^{n}, n=1,2) and of the last two normal intervals preceding the PVC (RR^{-n}, n=2,1) and is given by

$$TO = \frac{(RR^{+2} + RR^{+3}) - (RR^{-2} + RR^{-1})}{RR^{-2} + RR^{-1}} \times 100$$

where RR^{-2} and RR^{-1} are the first two normal intervals preceding the PVC and RR^{+2} and RR^{+3} are the first two normal intervals following the PVC. (Note that there are two intervals associated with the PVC; the normal-PVC interval, RR^{0} and the following PVC-normal interval and RR^{+1}.) Therefore, positive TO values indicate deceleration and negative TO values indicate acceleration of the sinus rhythm. Although the TO can determined for each individual PVC (and should be if performed on-line), TO has shown to lead to be more (clinically) predictive if the average value of all individual measurements is calculated. For the calculation of the mean TO the current version (1.11)

of the freely available HRT-algorithm [1] at least 15 normal intervals after each single PVC are required. TS is calculated by determining the steepest (linearly regressed) slope for the average sequence of the five consecutive normal intervals in the post-PVC `disturbed' tachogram (usually taken to be up to and RR^{+16}; the first 20 normal RR intervals). That is, all possible slopes from the set $\{RR^{+2, +3, \ldots, +6}, \ldots, RR^{+12, +13, \ldots, +16}\}$ are calculated, and the maximum of the 13 possible slopes is taken to be the TS.

Averaging: It is important that TS is calculated from an average time series composed of all the tachogram sections recorded around each ectopic beat. This helps average out short term oscillations and noise. Conversely, TO should be calculated for each section around the ectopic beat and then the resultant sections should be averaged. It is also important to use a sufficient number of sections over which to calculate these metrics. (A minimal number is usually considered to be of the order of 15 to 20 sections, but less have been used with success).

Rejecting artifacts: The criteria for excluding PVCs must be stringent, since HRT quantification can only deliver usable results if the triggering event was a true PVC (and not an artefact, T wave or similar artefact). In addition it must be ensured that the sinus rhythm immediately preceding and following the PVC is free from arrhythmia, artefacts and false beat classifications due to artefact. A useful set of exclusion criteria are:

I. Remove all RR intervals < 300ms or > 2000ms
II. Remove all RR^n where $|RR^n - RR^n| > 200$ms
III. Remove all RR intervals that change by more than 20% with respect to the mean of the 5 last sinus intervals (the reference interval)
IV. Only use PVCs with a minimum prematurity of 20%
V. Exclude PVCs with a post-extrasystole interval which is at least 20% longer than the normal interval.

TO values below 0 and TS values above 2.5 are considered normal, and abnormal otherwise. I.e. a healthy response to PVCs is a strong sinus acceleration followed by a rapid deceleration. Although the exact mechanism that leads to HRT is unknown, it is thought to be an autonomous baroreflex whereby the PVC causes a brief disturbance of the arterial blood pressure. When the autonomic control system is health, this rapid change causes an instantaneous response in the following RR intervals. If the autonomic control system is impaired, the magnitude of this response is either diminished or possibly completely absent. From a clinical perspective, HRT metrics have been shown to be predictive of mortality and possibly cardiac arrest. Furthermore, they have been shown to be particularly useful when the patients are taking beta-blockers: in one study combined TO and TS was found to be the only independent predictor of mortality compared to otherwise predictive markers such as mean HR, previous myocardial infarction and a low ejection fraction.

Other HRT metrics: Many other studies indicate that this technique is useful, and in particular the application of HRT analysis to study of the QT interval variation after PVCs has shown that QT interval turbulence occurs in association with HR turbulence. QT TO was defined as the relative difference between the QT interval of the first sinus cycle after an induced PVC and the mean of the QT intervals of the two sinus cycles preceding the premature beat. Savelieva *et al.* [5] found that patients with ischemic VT and left ventricular dysfunction exhibited significantly lower QT TO values than those with non-ischemic VT and normal ventricular function. The pattern of QT-interval turbulence is, in fact opposite to that of HR turbulence after a PVCs; that is, a large QT TO value is abnormal. Interestingly, neither induced APCs nor PVCs have shown observable QT TS dynamics. This may have been due to the analysis window being too short or due to the fact that the QT proxy that was used may have led to increased noise in the measurements. To date, the underlying mechanism of QT turbulence remains unclear.

In addition to HR and QT TO and TS, other HRT parameters that have been proposed include:

- *Turbulence dynamics*, [2]; The largest regressed slope between TS and heart rate in a particular individual over a sliding window of 10bpm.

- *Turbulence timing* [28]; The beat number of the 5 RR interval sequence used in the TS calculation at which the largest slope occurs.

- *Correlation coefficient of TS* [30]; the correlation coefficient of the regression line fitted to the 5 RR intervals giving the maximum slope (i.e., where TS is defined).

- *Turbulence jump* [31]; The maximum difference between adjacent RR intervals.

- *Turbulence frequency decrease* [37]; A frequency domain metric obtained by fitting a sine function to the post-compensatory pause.

Although many of these metrics have shown promise as independent disease predictors further studies are needed to ascertain whether any of these metrics provide significantly superior risk stratification to TO and TS. Furthermore, TO and TS are simpler to measure, and have been validated in large prospective studies. Further information is available from [1,3,38]

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