Dependence of premature ventricular complexes on heart rate — it’s not that simple

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Abstract

Introduction

Frequent premature ventricular complexes (PVCs) can lead to adverse health conditions such as cardiomyopathy. The linear correlation between PVC frequency and heart rate (as positive, negative, or neutral) has been proposed as a measure to guide treatment with beta-blockers. We evaluate the robustness of this measure to day-to-day variability and measurement methodology.

Methods

We analyzed 82 multi-day ECG recordings collected from 48 patients with frequent PVCs (burden 1-44%). For each record, the linear correlation between PVC frequency and heart rate was computed for different 24-hour periods, and using different time interval lengths to determine the PVC frequency and average heart rate.

Results

Using a 1-hour time interval, the correlation between PVC frequency and heart rate was consistently positive, negative or neutral on different days in 19.5% of patients. Using shorter time intervals, the correlation was consistent in 34.1-58.5% of patients. Using 1-minute time intervals emphasized a nonlinear dependence of PVC frequency on heart rate in most patients.

Conclusion

In patients with frequent PVCs, linear correlation of PVC frequency with heart rate is variable across different 24-hour periods and different interval lengths used to compute the average heart rate. The variable and often nonlinear dependence of PVC frequency on heart rate suggests that classification based on linear correlation should be used with caution.

Keywords

premature ventricular complexes, beta-blockers, Holter monitoring

I. Introduction

Premature ventricular complexes (PVCs) are a common finding in otherwise healthy patients [1]. If PVCs are frequent, there is a risk of progression onto heart failure [2]. In a study of patients with frequent PVCs, Winkle found that most patients displayed characteristic relationships between PVC frequency and heart rate. Most frequently there was a positive correlation (as assessed visually) in which there was a greater frequency of PVCs at faster heart rates, but in some patients, there could be a negative correlation, no correlation, or more complex relationships [3]. Winkle suggested that these findings may help explain why most patients have a reduction in PVC frequency when treated with beta-blocking agents.

Consistent with these early results, Hamon et al. found that a positive correlation between PVC frequency and heart rate is useful to select patients who will respond to beta blocker therapy [4]. However another study showed a conservative approach can be just as effective at reducing PVCs, and found no differential effect of beta blockers based on heart rate dependency [5]. Hamon et al. also found that patients with a positive correlation between PVC frequency and heart rate had a higher success rate to ablation therapy than patients with other characteristic relationships [6]. In carrying out their analyses, Hamon et al. considered the dependence by computing the Pearson correlation coefficient based on a 24-hour Holter recording in which the average PVC frequency and heart rate were determined over hour long intervals. These findings have recently been included in the European Society for Cardiology’s guidelines for managing patients with frequent PVCs [7].

Since the heart rate shows significant fluctuation on a time scale of minutes [8], subtle dependencies of PVC frequency on heart rate might be obscured by considering the average heart rate and PVC frequency over hour long intervals. In fact, Winkle’s initial studies considered the average heart rate and PVC frequency over one-minute rather than one-hour intervals. The effect of this interval length on the PVC-HR correlation has not been investigated. In addition, studies by Hamon and Winkle analyzed 24-hour Holter recordings, not permitting analysis of the variability of a patient’s PVC-HR correlation on different days.

In the current article, we investigate the robustness
of the PVC-HR correlation to (i) the time interval over which the PVC frequency and heart rate are measured and (ii) different 24-hour periods in multi-day records. We also determine how specific PVC rhythms (e.g., bigeminy) depend on heart rate and discuss the potential mechanisms involved.

II. Methods

A. Data Collection & Pre-processing

We collected 82 ECG recordings of 1-7 days from 48 patients with idiopathic frequent PVCs using a wearable device (Icentia CardioSTAT) at the University of British Columbia [9]. Beat type and timing were obtained using Icentia’s beat detection algorithm. For interval lengths of 1 minute, 10 minutes, and 1 hour, we compute total number of PVCs and the average heart rate. Unidentifiable beats were omitted from the calculation of the average heart rate for each interval. To facilitate comparison across intervals, PVC count was adjusted to represent the expected count over an hour long interval.

The cohort had a mean age of 63.5 years (range 32-91) with 37.5% females. The PVC burden (PVCs over total number of beats) at the time of the 7-day patch monitor was a median of 14.5% (range 1-44%). The mean left ventricular ejection fraction (LVEF) was 52.3% (range 25-72%) with 16/48 (33.3%) having an LVEF of < 50%. Of these 16 patients with impaired LV function, 14 (29.17%) had non-ischemic left ventricular dysfunction, 1 (2.1%) had an ischemic cardiomyopathy and 1 (2.1%) had a mixed valvular and non-ischemic cardiomyopathy.

B. Statistical Analysis

We compute the Pearson correlation coefficient and linear regression of PVC count against heart rate. The Pearson correlation coefficient is a measure of linear association between the two variables, computed as

\[ r = \frac{\text{Cov}(X, Y)}{\sigma_X \sigma_Y} \]  

where \( \text{Cov}(X, Y) \) is the covariance between the heart rate \( X \) and the PVC count \( Y \), and \( \sigma \) is the standard deviation. A \( t \)-test is used to obtain the corresponding \( p \)-value. Linear regression determines the line of best fit between the variables. We use the ordinary least squares solution, whose slope is given by

\[ B = \frac{\text{Cov}(X, Y)}{\sigma_X^2}. \]  

Each patient is classified as having a positive \((r > 0, p < 0.05)\), negative \((r < 0, p < 0.05)\) or neutral correlation \((p > 0.05)\) as in Hamon et al. [4, 6]. Classifications are made for each 24-hour section and for the whole recording.

Variability of the classification to different days is quantified using the entropy function

\[ H(j) = -\sum_{c_j \in C} p(c_j) \log_2 p(c_j) \]  

where \( p(c_j) \) is the proportion of days for which a patient \( j \) was assigned class \( c_j \) and \( C \) is the set of all possible classes (positive, negative, neutral). We normalize the entropy to be between 0 and 1. A low value (0) indicates a consistent classification on each day whereas a high value (1) indicates an inconsistent classification.

In addition to the average heart rate and PVC count, we determine the PVC rhythms, as defined by the number of intervening sinus beats (NIBs) between consecutive PVCs. For example, an NIB of one corresponds to bigeminy (alternating sinus beats and PVCs). An NIB of two corresponds to trigeminy etc. We compute the NIB values and the heart rates at which they occur across the whole record and plot the distribution of NIB values as a function of heart rate.

All processing and analysis scripts used in this study are publicly available at the Github repository https://github.com/aosakwe/PVC-HR.

III. Results

A. Impact of time interval length

Most recent studies that evaluate the dependence of PVC frequency on heart rate use a 1-hour time interval to compute the PVC count and average heart rate [4, 6, 9-12]. We show this approach for three patients that fall into the positive, negative and neutral classes, respectively in Fig. 1A-C. Using a shorter time interval yields more data points and a wider distribution of PVC counts and heart rates (Fig. 1D-I). This is expected as shorter time intervals capture brief moments of particularly fast or slow heart rates that would otherwise be averaged out. Observing PVC count with a shorter time interval reveals (i) nonlinearities in the relationship between PVC count and heart rate (e.g. the inverted parabola in Fig. 1G) and (ii) structure via regions of high density (e.g. the positive linear trend at high PVC count in Fig. 1H). These nonlinearities and regions of high density are also present when plotting data for the full 7-day recordings (Sup. Fig. 1) and challenge the feasibility of using linear correlation as a classification metric.

Modifying the time interval length can result in a different classification. In patient MC136 (Fig. 2), using a 1-hour interval resulted in a neutral classification on the first and third day. In contrast, using a 1-minute interval resulted in a negative classification on day 1 and a positive classification on day 3. In general, we find that shorter time intervals reduce the number of neutral classifications in the cohort (Table 1). This is due to correlation
FIG. 1: Dependence of PVC frequency on heart rate for three patients using different length time intervals. Panels show PVC count and average heart rate from 1-hour (A,B,C), 10-minute (D,E,F) and 1-minute (G,H,I) intervals during the first 24 hours in the record. PVC count is scaled to the expected number of PVCs in one hour to facilitate comparison across time intervals. Lines show the linear regression with 95% confidence intervals. Correlation of PVC count with heart rate is positive (blue), negative (red) or neutral (gray). Inset shows Pearson’s correlation coefficient ($r$) and slope of the linear regression ($b$).

<table>
<thead>
<tr>
<th>Class</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
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<td>44%</td>
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<td>41%</td>
<td>43%</td>
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<td>47%</td>
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<tr>
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<td>14%</td>
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<td>12%</td>
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<td>8%</td>
<td>11%</td>
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<tr>
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<td>44%</td>
<td>45%</td>
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<th>Day 5</th>
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<td>58%</td>
<td>58%</td>
<td>51%</td>
<td>54%</td>
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<td>57%</td>
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<td>21%</td>
<td>21%</td>
<td>16%</td>
<td>19%</td>
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<tr>
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<td>28%</td>
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<th>Day 4</th>
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<td>74%</td>
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<tr>
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<td>18%</td>
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<tr>
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<td>13%</td>
<td>8%</td>
<td>10%</td>
<td>16%</td>
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TABLE I: Distribution of classifications on each day for different time interval lengths over 82 records.

B. Variability across different 24-hour periods

Previous studies have computed PVC-HR correlation for 24-hour Holter records [3, 4, 6, 10–12]. We have recordings of up to 7 days, allowing us to assess PVC-HR correlation on different days. Patient MC136 receives different classifications on different days regardless of the time interval length used (Fig. 2). While some patients receive the same classification on each day, many receive different classifications (Fig. 3, Sup. Fig. 2). We quantify classification variation in terms of entropy. Zero entropy corresponds to a consistent classification each day, whereas a non-zero entropy corresponds to an inconsistent classification. Using 1-hour time intervals, 80.5% of patients have a non-zero entropy i.e. their classifications vary. Using 10-minute and 1-minute intervals, the percentage of patients is 65.9% and 41.5%, respectively. Using a shorter time interval results in lower day-to-day variability of classifications. Although classifications in individual patients vary throughout the week, the distribution of classifications on different days is similar (Table 1).

The set of daily classifications for a patient can be

being computed on a larger amount of data, resulting in tighter confidence intervals (Fig. 1) and smaller $p$-values.
FIG. 2: Dependence of PVC frequency on heart rate for patient MC136 on different days and using different length time intervals. For further details, refer to the caption of Fig. 1.

viewed as a point on a ternary plot, which graphically depicts the ratios of positive, negative and neutral classifications. Figure 4 shows the distribution of these points for the cohort. Using a 1-hour interval, most patients receive a combination of positive and neutral classifications over the week. Using a 10-minute interval, there are no longer any patients who receive a consistent neutral classification. Using a 1-minute interval, positive and negative classifications are more consistent, with 58.5% of patients receiving the same classification on each day. We also consider classifications using the full multi-day record and compare this to the set of classifications made on each day. Using a 1-hour interval, 64.4% of the daily classifications are consistent with classifications using the full record. In contrast, using a 1-minute interval, 82.2% are consistent, indicating that shorter time intervals result in classifications on 24-hour periods that are more consistent with what one would obtain using a 7 day recording. In addition, classification using the full record resulted in fewer neutral and more positive classifications, regardless of the time interval used (Sup. Fig. 3).

C. Rhythms contributing to the PVC-HR relationship

In many patients, we observe a nonlinear relationship between PVC burden and heart rate (e.g. Fig. 5A). This is related to the appearance and disappearance of particular PVC rhythms at different heart rates. To investigate these rhythms, we compute the distribution of NIB values at different heart rates. How these rhythms depend on heart rate may be indicative of an underlying mechanism for the PVCs.

Patient MC155 (Fig. 5A-B) shows a parabolic dependence of PVC frequency on heart rate, with a turning point around 75 bpm. Data at lower heart rates have a strong positive correlation ($r = 0.84$) and data at higher heart rates have a negative correlation ($r = -0.35$). This phenomenon was observed for each day of the recording. At slow heart rates ($< 64$ bpm), PVCs occur infrequently and most often in a bigeminal rhythm (NIB=1). This may be a manifestation of the “rule of bigeminy” associated with triggered activity and reentry, where the occurrence of a PVC results in a longer cycle due to a skipped beat, favoring a subsequent PVC and a repeating rhythm.
FIG. 3: Variability of PVC-HR classification over different days. (A–I) Pearson correlation coefficient and PVC-HR classification as positive (blue), negative (red) or neutral (gray) on different days for 9 patients. Classifications using 1-hour intervals. (J) Variation in PVC-HR classification for each record (row) using time intervals of different lengths (columns). Variation is quantified using (normalized) entropy which goes from zero (yellow) to one (black). Patients with low entropy have a consistent classification (e.g. A). Patients with high entropy have an inconsistent classification (e.g. C).

FIG. 4: Distribution of classification sets for each patient using different interval lengths. A classification set contains each 24-hour classification of a patient and is positioned on the triangle according to the ratios between each classification frequency. A patient with the same classification on each day would be placed in a corner. The distribution is shown using a ternary density plot with red (white) representing a high (low) concentration of patients.

[13, 14]. At faster heart rates the patient displays a variety of different rhythms, notably an abrupt occurrence of trigeminy (NIB=2) at around 70 bpm.

Patient MK284 (Fig. 5C-D) shows a structured dependence of PVC frequency on heart rate. Though classified as neutral, this patient shows two regimes of PVC dependence. One with very few PVCs independent of heart rate, and another with more abundant PVCs that become more frequent at higher heart rates. The PVCs primarily occur in a trigeminal rhythm, with
quadrigeminy becoming significant for heart rates $>88$ bpm and bigeminy becoming significant for heart rates $<80$ bpm.

IV. Discussion

We assessed the robustness of linear correlation between PVC frequency and heart rate as a metric to classify patients with frequent PVCs. Using shorter time intervals to compute average heart rate and PVC frequency increased the number of data points, resulting in a more significant Pearson correlation coefficient and fewer patients being classified as neutral. It also revealed PVC frequencies at more extreme heart rates, which usually did not conform to a linear trend. When investigating robustness of PVC-HR correlation to different days, we found that the majority of patients did not receive the same classification on each day. Using a shorter time interval improved consistency, but left some patients still receiving both positive and negative classifications. The day-to-day variability and nonlinear dependence of PVC frequency on heart rate suggests caution when using linear correlation as a classification tool for treatment groups, particularly with 24-hour Holter recordings. Further work should develop and test alternative classification metrics and their robustness.

An apparent contradiction is that shorter time intervals reveal nonlinear properties of the PVC-HR relationship, yet result in a more significant Pearson correlation coefficient (smaller $p$-value). This may be understood by the fact that shorter time intervals generate a larger number of data points, and most of these data lie within a short range of heart rates where the data is approximately linear. An interesting avenue for future research is to evaluate the PVC-HR relationship during exercise tests where a larger portion of the data come from faster heart rates.

There are many factors besides heart rate that can impact the frequency of PVCs [15]. For example, PVC frequency can vary with autonomic tone [16, 17], exercise [18], caffeine intake [19], and the time of day [9]. These factors could play an important role in the observed PVC dependence on heart rate. To better study their interplay, ambulatory monitoring with patients that track their activity and consumption will be beneficial.

The dependence of PVC frequency on heart rate necessarily reflects the underlying mechanism for the PVCs.
For example, for pure parasystole the number of PVCs at any heart rate is proportional to the fraction of time that the ventricle is not refractory [20]. This fraction is greater at slower heart rates, resulting in a negative linear correlation between the frequency of PVCs and heart rate [21]. In contrast, for situations in which the parasystolic focus is reset by the sinus rhythm, more complex relationships between sinus rate and PVC frequency occur since heart rates at which no PVCs occur can be sandwiched between heart rates that generate frequent PVCs [21–23]. Reentry and triggered activity are mechanisms that are associated with the “rule of bigeminy”, where a bigeminal rhythm of alternating sinus beats with PVCs is self-perpetuating. A patient with persistent bigeminy over a range of heart rates would have a linear dependence of PVC frequency on heart rate with a slope of 0.5. Determining the mechanism of PVCs from observation of their dynamics is a challenging inverse problem where insights can be gained from mathematical [21, 22, 24] and biological [23, 25] models.

As originally observed by Winkle [3], the relationship between PVC frequency and heart rate is complex. This makes it difficult to obtain a robust classification of PVC dependence on heart rate using linear correlation, which may provide partial reason for the conflicting reports on the efficacy of beta blockers for treating PVCs [4, 5]. Recent advances in wearable device technology have revolutionized data collection capabilities [26]. Coupled with the power of modern computing systems, opportunities arise to study the complexity of PVC dependence on heart rate in greater depth, which may lead to mechanistic insight.

A. Limitations

This is a retrospective study without data on clinical outcomes. No attempt was made to evaluate the correlation between PVC frequency and heart rate for each PVC morphology. Interpolated PVCs can result in over-estimation of the heart rate, though were very uncommon. Finally, some records had regions of unidentifiable beats due to noise or artifact, which limited the amount of data available. Future analyses will benefit from improvements to wearable device technology and beat identification algorithms.

V. Conclusion

The dependence of PVC frequency on heart rate is often nonlinear, can vary on different days, and can vary based on the length of the time interval used in its computation. Therefore, linear correlation between PVC frequency and heart rate as a means to determine treatment groups should be used with caution.

Acknowledgments

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Supplementary Figure 1: Dependence of PVC frequency on heart rate for three patients using data from the entire multi-day recording. For further details, refer to the caption of Fig. 1.

Supplementary Figure 2: Variability of PVC-HR classification over different days for three patients, using different time intervals. For further details, refer to the caption of Fig. 3.
Supplementary Figure 3: Comparison of distribution of classifications when using 24-hour periods vs. using the entire recording.