Risk-Stratification following Acute Coronary Syndromes Using a Novel Electrocardiographic Technique to Measure Variability in Morphology

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Abstract

We propose a new technique that quantifies the extent to which subtle ECG morphology changes exist from beat to beat. Termed morphological variability (MV), this variable measures changes in the shape and timing characteristics of cardiac events in sequential pairs of heart beats. In contrast to other techniques that focus on one specific aspect of the ECG, our approach integrates information from all waves and intervals in the beat, with the goal of providing a more global assessment of cardiac electrical performance. When tested on 400 patients following ACS, an increased risk of death was seen during a follow-up period of 90 days for patients with high MV (HR=5.96;p=0.002). This relationship could be observed even after adjusting for HRV measures (adjusted HR=3.56;p=0.05).

1. Introduction

An extensive literature exists on the subject of heart rate variability (HRV) applied to ECG signals [1]. HRV provides a non-invasive means to assess autonomic modulation of sinus node activity. Since the autonomic system has an influence on the rate at which the heart beats, observing the variation in the length of RR intervals over time provides insight into sympathetic and parasympathetic stimulation of the heart. This information may have prognostic value in identifying patients at risk for increased cardiac mortality.

While a variety of metrics have been proposed to calculate HRV, including time-domain, frequency-domain and non-linear approaches, these metrics are unified in that they only use information related to the length of the RR intervals. They do not include information associated with how the shape of the heart beats changes from beat to beat.

We extend the process of studying variability in the length of heart beats with an analogous approach to study variability in the morphology of heart beats. This work is motivated by a belief that subtle changes in morphology might be indicative of electrochemical abnormalities within the myocardium that are potentially proarrhythmic [2]. The resulting risk measure produced by measuring this effect is termed the *morphologic variability* (MV).

2. Methods

For every pair of consecutively occurring beats in the ECG signal, differences in morphology are quantified by calculating an "energy difference" between the beats. The simplest way to calculate this energy difference is to simply subtract the samples of one beat from another. However, if samples are compared based strictly on their distance from the start of the P-wave, this process may end up computing the differences between samples associated with different waves or intervals. For example, consider the two heart beats depicted in Figure 1. In the drawing on the left, samples are aligned based on their distance from the onset of the P-wave. One consequence of this is that samples that are part of the T-wave of the top beat are compared with samples not associated with the T-wave of the bottom beat. A measure computed this way will not reflect differences in the shapes of the T-waves of adjacent beats

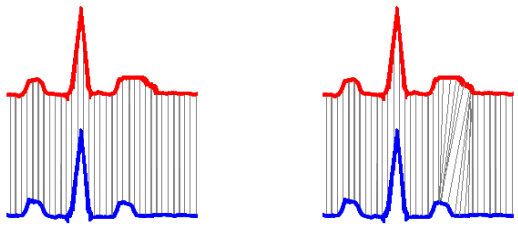


Figure 1. Alignment of beats by dynamic time-warping. On the left, samples are aligned by index. This may lead to energy differences being calculated across inconsistent parts of the two signals. Conversely, on the right, the dynamic time-warping algorithm produces the optimal alignment of the two sequences and ensures a more a consistent measure of energy differences

We use a variant of dynamic time-warping (DTW) [3] to align samples that correspond to the same kind of underlying physiological activity. As depicted in the drawing on the right side of Figure 2, this can require aligning a single sample in one beat with multiple samples in another beat. The algorithm uses dynamic programming to search for an alignment that minimizes the overall distortion. Distortion is measured using the method described in [4], which captures differences in both amplitude and timing of ECG waves.

More precisely, given two beats, x_1 and x_2, of length l_1 and l_2 respectively, DTW produces the optimal alignment of the two sequences by first constructing an l_1-by-l_2 distance matrix d. Each entry (i,j) in this matrix d represents the square of the difference between samples $x_1[i]$ and $x_2[j]$. A particular alignment then corresponds to a path, φ through the distance matrix of the form:

$$\varphi(k) = \left(\varphi_1(k), \varphi_2(k)\right), \quad 1 \le k \le K \tag{1}$$

where φ_1 and φ_2 represent row and column indices into the distance matrix, and K is the alignment length.

The optimal alignment produced by DTW minimizes the overall cost:

$$C(x_1, x_2) = \min_{\varphi} C_{\varphi}(x_1, x_2) \tag{2}$$

where C_{φ} is the total cost of the alignment path φ and is defined as:

$$C_{\varphi}(x_1, x_2) = \sum_{k=1}^{K} d(x_1[\varphi_1(k)], x_2[\varphi_2(k)]) \tag{3}$$

The search for the optimal path is carried out in an efficient manner using dynamic programming. The final energy difference between the two beats x_1 and x_2, is given by the cost of their optimal alignment, and depends on both the amplitude differences between the two signals, as well as the length K of the alignment (which increases if the two beats differ in their timing characteristics). In this way, the technique described here measures changes in morphology resulting from both amplitude and timing differences between the two beats.

The process described above transforms the original ECG signal from a sequence of beats to a sequence of energy differences. This new signal, comprising pair-wise, time-aligned energy differences between beats, is then smoothed using a median filer of length 8. We call the resulting times series the morphologic distance (MD) for the patient.

The morphologic variability (MV) for a patient can be calculated from the MD time-series using metrics commonly employed in HRV analysis. An advantage of this approach is that it allows us to more directly understand the potential of morphology to yield information beyond that supplied by analysis of RR intervals.

Two of the most widely used HRV measures are the time-domain metric SDANN (the standard deviation of the average of five minute windows of the time-series) and the frequency-domain metric LF/HF (the average ratio of the power in the frequency spectrum of five minute windows of the time-series between 0.04–0.15 Hz and 0.15–0.4 Hz). We compute similar measures using the MD time-series, yielding two distinct MV measures, MV-SDANN and MV-LF/HF.

3. Results

We calculated MV and HRV measures within 48 hours of ACS for 400 randomly selected patients in the MERLIN trial [5]. Patients were dichotomized at both the 80th and 90th percentiles for MV-SDANN and at the 10th and 20th percentiles for HRV-SDANN. In the case of the LF/HF measure, which is not a direct measure of variability and instead measures the balance between the low frequency and high frequency components of the underlying time-series, patients were dichotomized at the 10th and 20th percentiles for both MV and HRV.

Table 1 presents the results of univariate association between these risk measures and death over a 90 day follow-up period. In the case of heart rate variability, HRV-LF/HF at both the 10th and 20th percentile showed a highly statistically significant association with the endpoint of death over the 90 day period following ACS. The LF/HF measure was a better risk-stratifier than the SDANN measure. Replacing the HRV metrics used here with other metrics (i.e., SDNN, ASDNN, HRVI, BETA) did not improve the results.

For morphologic variability, MV-LF/HF was highly associated with death at both the 10th and the 20th percentile cutoff. As was the case for HRV, the LF/HF measure for MV performed consistently better than the SDANN measure.

Table 1. Univariate association between different HRV and MV measures and death following ACS in 90 days.

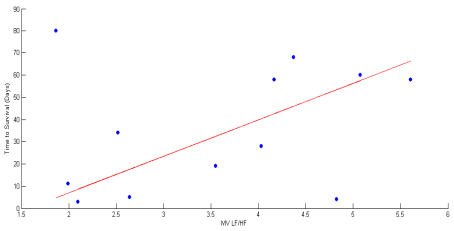
Parameter	Hazard Ratio (P-value)
HRV-SDANN	
HRV-SDANN (20%)	4.11 (0.014)
HRV-SDANN (10%)	1.86 (0.424)
HRV-LF/HF	
HRV-LF/HF (20%)	5.90 (0.002)
HRV-LF/HF (10%)	6.90 (0.001)
MV-SDANN	
MV-SDANN (80%)	0.36 (0.321)
MV-SDANN (90%)	0.80 (0.833)
MV-LF/HF	
MV-LF/HF (20%)	5.96 (0.002)
MV-LF/HF (10%)	7.15 (0.001)

Table 2. ROC c-statistic for different HRV and MV measures and death following ACS in 90 days.

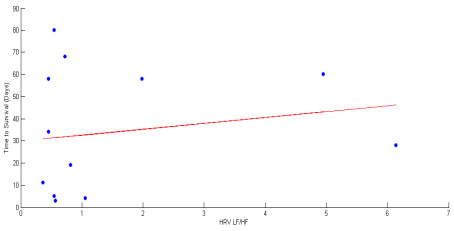
Parameter	ROC c-statistic
HRV-SDANN	0.62
HRV-LF/HF	0.70
MV-SDANN	0.59
MV-LF/HF	0.75

Table 3. Multivariate association between MV-LF/HF and different HRV measures for death over 90 days.

Parameter	Hazard Ratio (P-value)
Model 1	
HRV-SDANN (20%)	2.86 (0.078)
MV-LF/HF (20%)	4.68 (0.011)
Model 2	
HRV-SDANN (10%)	1.12 (0.819)
MV-LF/HF (10%)	6.96 (0.001)
Model 3	
HRV-LF/HF (20%)	3.51 (0.053)
MV-LF/HF (20%)	3.56 (0.050)
Model 4	
HRV-LF/HF (10%)	3.79 (0.050)
MV-LF/HF (10%)	3.99 (0.042)



(a) MV-LF/HF (Y = -25.69 + 16.38 X; p = 0.015)



(b) HRV-LF/HF (Y = 29.92 + 2.66 X; p = 0.696)

Figure 2: Robust regression of MV-LF/HF and HRV-LF/HF against the survival time for patients who died during the first three months following NSTEACS. The linear model shown in each case (red) is derived by means of iteratively reweighted least squares with the bisquare weighting function.

Our results show that for both HRV-LF/HF and MV-LF/HF the relationship between the risk variable and death was generally even more pronounced at the lowest decile than at the lowest quintile. This suggests that there is a graded response whereby the risk of death increases the lower each metric is. For the period examined, the MV-LF/HF risk variable dichotomized at the 10th percentile showed the strongest association with the endpoint of death.

We also calculated the ROC c-statistics for the different risk variables and the endpoint of death. The results of this analysis are shown in Table 2.

The ROC c-statistics for the different risk variables and the endpoint of death over multiple time periods are shown in Table 2. The c-statistics for both HRV-LF/HF and MV-LF/HF exceeded the threshold of 0.7 associated with clinical utility [6].

To test whether an analysis of the entire beat, as opposed to a particular segment of the ECG signal is important for achieving these results, we also analyzed the contribution of each segment of the ECG signal (e.g., ST segment or QT interval) to the overall MV-LF/HF value. We found that no one segment was predominant in its overall effect on MV-LF/HF (data not shown). In short, the entire signal is needed to obtain the results reported here.

The results of multivariate analysis for the MV-LF/HF measure with the different HRV metrics is shown in Table 3. In the multivariate models, MV-LF/HF was the only risk variable significantly associated with the endpoint of death at the 20th percentile cutoff. At the 10th percentile cutoff, both MV-LF/HF and HRV-LF/HF were independently associated with death in the multivariate model, suggesting that HRV and MV provide complementary information. This is consistent with our assumption that they provide measures of different physiological activity.

Figures 2(a) and 2(b) plot the MV-LF/HF and HRV-LF/HF risk variables against the survival time for patients who died within 90 days of ACS. In these cases, MV-LF/HF showed a statistically significant linear association between the risk variable and the time to survival for patients. A unit increase in MV-LF/HF was correlated with a 16 day increase in the survival time of these patients (p=0.015). In the case of HRV-LF/HF, the relationship between the risk variables and the survival time was weaker.

4. Discussion and conclusions

In this paper, we investigate supplementing information in the variability of RR intervals in an ECG signal with variability of beat shape from beat to beat. We introduce morphologic variability (MV) as a measure of global variation in the ECG morphology. We approach

the problem of calculating MV in a manner analogous to HRV. Specifically, just as HRV measures are computed from a time-series that describes variations in heart rate or RR intervals, MV measures are computed from a morphologic distance (MD) time-series that describes differences between the morphology (or shape) of adjacent beats as measured by dynamic time-warping. Time domain statistical measures such as SDANN then use the raw MD or RR time-series to compute metrics that describe variability while frequency domain measures such as LF/HF derive the power spectrum and measure the difference between low frequency and high frequency content.

Our hope was to design a measure that would detect signs of ischemia associated with subtle morphologic changes throughout the entire ECG signal that are not commonly appreciated in clinical practice [7-8]. Even in the absence of overt signs of ischemia, subtle ECG changes may indicate electrochemical abnormalities within the myocardium that are potentially proarrhythmic [2]. Given this, we hypothesized that an automated procedure for identifying subtle morphologic changes between successive beats in a surface ECG signal would provide additional data that could be used to identify patients at high risk following ACS.

We investigated the potentially complementary information provided by MV and HRV in risk-stratifying patients at increased risk of cardiac mortality following acute coronary syndromes (ACS). In our study, we found MV-LF/HF did indeed have a highly significant association with death in this cohort. In fact, in this cohort, MV-LF/HF was more significantly correlated with death than any of the HRV measures. We did not, however, find an association between MV-SDANN and death in this cohort. This might seem surprising; especially in conjunction with the finding that HRV-SDANN was found to be associated with death in this cohort. The difference stems from the fact that calibration errors do not affect the measurement of the QRS complex and do not have a significant impact on the estimation of HRV. However, in the case of MV time-domain metrics, they may lead to some patients appearing to have more or less energy in their beat-to-beat differences. This is not a case with the use of the LF/HF metric, which is a ratio and inherently normalizes the score for each patient.

The results reported here suggest strongly that that a low MV-LF/HF ratio is significantly, and independently, associated with an increased risk of death in the subsequent short and long term periods following hospital admission for NSTEACS. Information in the MV-LF/HF score may be further supplemented by HRV-LF/HF and HRV-SDANN metrics in multivariate models.

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