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Measures of Cardiac Contractility Variability during Ischemia

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Abstract— Acute myocardial infarction (AMI) is one of the leading causes of death in the US. While heart rate variability (HRV) has been widely studied for ischemia detection, the changes in cardiac contractility variability have not yet been explored. This paper presents novel variability analysis using 23 linear and non-linear measures during myocardial ischemia. Multiple physiologic measures of cardiac contractility and heart rate variability are analyzed and compared before and after acute coronary artery occlusion in a swine model. Change in the spread of the Poincare plot of RR intervals was highly negatively correlated with the change in contractility reflective of ischemia ($r=-0.92$, $p<0.05$). The change in approximate entropy of the S1 heart sound intensity was also highly correlated ($r=0.96$, $p<0.05$) with the change in contractility due to ischemia. These preliminary results show the potential utility of nonlinear measures of variability to detect changes in the autonomic tone due to ischemia. These parameters, if measured continuously, may be used for early detection of AMI events in patients with implantable devices. Further research in a larger clinical study is warranted to confirm these findings.

I. Introduction

Acute myocardial infarction (AMI) is one of the leading causes of death in the US affecting about 800,000 people [1]. Although over 90% of people who are hospitalized with an AMI survive, about 250,000 die before presentation to a hospital. A reliable method to detect the onset of AMI is desired to improve patient care and outcome.

Heart rate variability (HRV) has been widely studied for ischemia detection. In [2], different metrics of HRV, including the low and high frequency powers, are shown to be significantly different in patients with ischemic angina when compared to controls. A time-frequency based analysis of HRV is used to understand the patterns of change during ischemia in [3]. While HRV has been well studied in the context of ischemia the focus of the variability research has been limited to RR interval analysis.

In this paper multiple left ventricular (LV) hemodynamic metrics are studied. Well known cardiac contractility measures from LV hemodynamics are used, including the LV max dP/dT and the S1 heart sound amplitude. While the LV pressure based parameters are invasive measurements, the S1 amplitude is known to be a non-invasive correlate of cardiac contractility [4]. The different variability measures investigated in this study are based on typical HRV metrics. For years these metrics have been used to study the relationship between the autonomic nervous system and the cardiovascular system. The most common HRV measures used are those derived from time domain variability and frequency domain power relationships. More recently HRV analysis is being performed using novel non linear measures [5].

In this paper we present novel variability analysis of 23 linear and non-linear measures during ischemia. Multiple measures of cardiac contractility variability and heart rate variability are analyzed and compared to the LV contractility change due to ischemia. We show that a number of these variability measures are highly correlated to the LV performance deterioration during ischemia. These parameters may be useful to detect such ischemic events when measured from an implanted device.

II. Methods

A. Animal Model

Physiologic data were collected during an acute myocardial ischemia induction in a pre-clinical setting. The study complied with all animal use regulations as set forth in the Animal Welfare Act, Title 9, CFR, Chapter 1, Subchapter A and adhered to the principles outlined in the "Guide for the Care and Use of Animals," National Institutes of Health Publication. Acute myocardial ischemia was created using a coronary artery balloon occlusion protocol. The swine model was selected because of the similarity to the anatomical geometry, scale, and extent of arterial collateral branching to the human. Since phenylephrine, epinephrine and dobutamine impact the degree of ischemia, their usage was maintained at a minimal level during the study and were administered under the consensus of the facility veterinarian.

The animals were sedated, intubated and placed on a volume-controlled ventilator. Oxygen and isoflurane levels were set as determined appropriate by the facility veterinarian and adjusted as needed to maintain a surgical plane of anesthesia. The animals were also given heparin and anti-arrhythmic drugs per protocol. After baseline data collection, a guide wire was introduced in the pre-specified artery. An angioplasty balloon of appropriate size and length for the specified artery was then positioned in the pre-specified location. The balloon was inflated for as long as tolerated by the animal up to 60 minutes. One of the two coronary arteries was occluded in one study: left anterior descending artery and left circumflex artery. The average

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pre-occlusion data collection time was 58 minutes and the average balloon occlusion time was 42 minutes.

Additionally necropsy was performed after the animal was euthanized to evaluate the ischemic mass of the left ventricle expressed as a % of the LV mass. Figure 1 shows the level of ischemia that was achieved in the six swine that underwent the protocol.

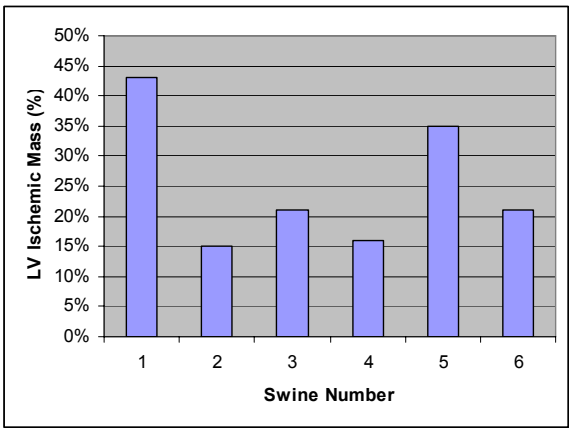

Figure 1: The left ventricular ischemic mass measured during necropsy

B. Physiologic Measurements

The following physiologic data were collected during the study: left ventricular pressures from invasive catheters (Millar Instruments, Houston, Texas), heart sounds from a proprietary surface accelerometer and electrocardiogram (ECG). All signals were synchronously recorded at 1kHz. Measurements extracted from the three signals consisted of amplitudes and timing intervals.

ECG measurements: *RR intervals* were measured from the ECG signal. The R peak detector described in [6] was used to identify the R peak timings. These detected R peaks were also used to cue the hemodynamic measurements from LV pressure and heart sounds. The RR intervals were also used for the HRV calculations.

LV Pressure parameters: The LV pressure signal was first parsed using the R wave markers to extract individual beats. Each beat was then differentiated to generate the LV dP/dT signal. Using a 200 ms window starting after the R peak location the max value of the LV dP/dT (max dP/dT) was extracted. Max dP/dT is used in this paper as the reference measure to quantify the reduction in LV performance (contractility) due to ischemia.

S1 amplitude: A detailed description of the algorithm used to measure the S1 amplitude is presented in [7]. A summary of the steps is shown in Figure 2. First each heart sound beat was parsed using the R peak marker. Each parsed waveform was then filtered with a band-pass filter with cut-off frequencies between 20 Hz and 90 Hz. A 250ms window after the R peak was used to measure the candidate S1 peaks. A dynamic programming based tracking algorithm was then used to measure the largest, most consistent S1 peak for the duration of the animal study.

C. Variability Analysis

The RR interval, max dP/dT and S1 amplitude data were parsed into 5-minute epochs. Twenty three variability parameters were calculated for each 5 minute epoch. These included 11 time domain metrics: mean, median, standard deviation of normal-to-normal beats (SDNN), inter-quartile range of normal-to-normal beats (IQRNN), coefficient of variation (CV), standard deviation of successive differences (SDSD), inter-quartile range of successive differences (IQRSD), normalized IQRSD (NIQRSD), root-mean-square of successive differences (RMSSD), coefficient of variation for successive differences (CVS) and percentage of differences between adjacent normal-to-normal intervals that are >50 msec (pNN50); 4 frequency domain metrics: power in the high- and low-frequency range (HF, LF), power ratio (LF/HF), and total power; 3 time-frequency metrics: high- and low-frequency wavelet power (HFW, LFW) and power ratio (LFW/HFW); and 5 nonlinear metrics: approximate entropy (ApEn), X-Y scatter from Poincare plot (SigXY), fractal dimension (FD), and detrended fluctuation analysis (DFA1 and DFA2). These metrics are described in [5].

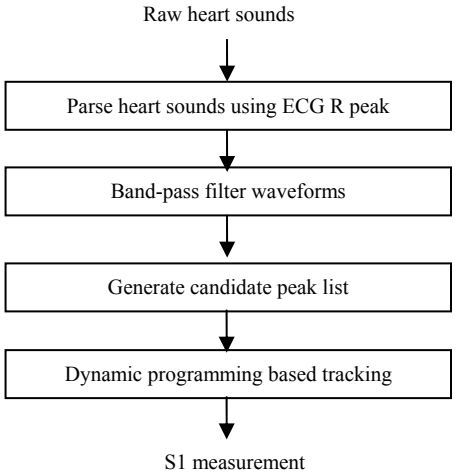

Figure 2: Algorithm for S1 measurements.

III. Results

A. Case Study

A representative dataset is presented to show the relationships between the different parameters (RR interval, max dP/dT and S1 amplitude) and select variability metrics. Figure 3 shows the max dP/dT, RR interval and S1 amplitude along with the two non-linear variability metrics that we found to be most predictive of changes in LV performance (max dP/dT) due to ischemia. During the course of the study the max dP/dT decreased; dropping significantly post occlusion. The balloon inflation resulted in a reflex increase in contractility possibly due to the autonomic compensatory mechanisms. This was also seen in changes in RR interval and the SigXY derived from RR intervals. Periods immediately after the balloon inflation

had relatively higher SigXY again possibly due to an autonomic reflex. As expected the S1 amplitude was correlated with changes in max dP/dT.

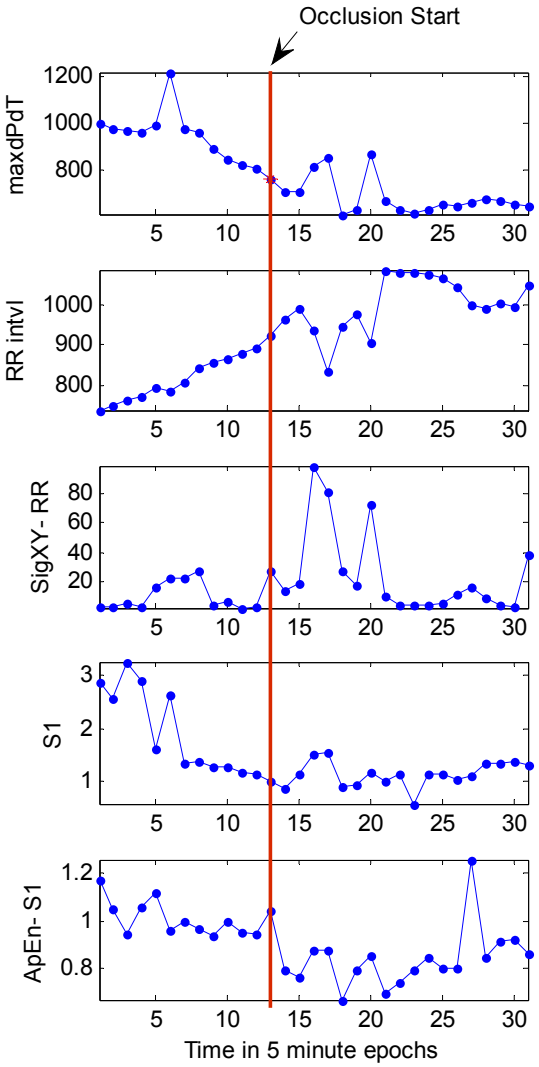

Figure 3: Examples of the different parameters measured before and after balloon occlusion.

B. Variability comparison with LV contractility change

During the ischemia protocol the LV contractility, as measured by the max dP/dT, reduced on an average by 18.5%. No consistent relationship was found between the ischemic mass measured during necropsy and the change in max dP/dT. To evaluate changes due to ischemia we used the change in max dP/dT as the reference for the LV contractility change.

HRV metrics: The 23 metrics listed in Section II-C were measured for the RR intervals from all 5 minute epochs during the protocol. The change in these metrics before and after occlusion was compared to the change in max dP/dT.

We found that many of the variability metrics were well correlated to the change in max dP/dT across the 6 animals. Figure 4 shows the relationships between changes in selected HRV metrics and changes in max dP/dT. A summary of all the relationships between changes in RR interval based variability metrics and max dP/dT is shown in column 2 in Table 1. While linear measures of RR intervals showed moderate correlation with max dP/dT (r ~ 0.7), some of the nonlinear measures, such as the X-Y spread from a Poincare plot (SigXY) of RR intervals, showed a higher correlation with max dP/dT (r= -0.92). These scatterplots highlight that while the RR intervals may not be highly correlated to changes in contractility during ischemia the variability parameters (e.g. SigXY) may provide additional predictive information.

S1 amplitude metrics: The 23 metrics listed in Section II-C were also measured for the S1 amplitude for all 5 minute epochs during the protocol. The change in these metrics before and after occlusion was next compared to the change in max dP/dT. Figure 5 shows the relationships between changes in selected S1 variability metrics and changes in max dP/dT.

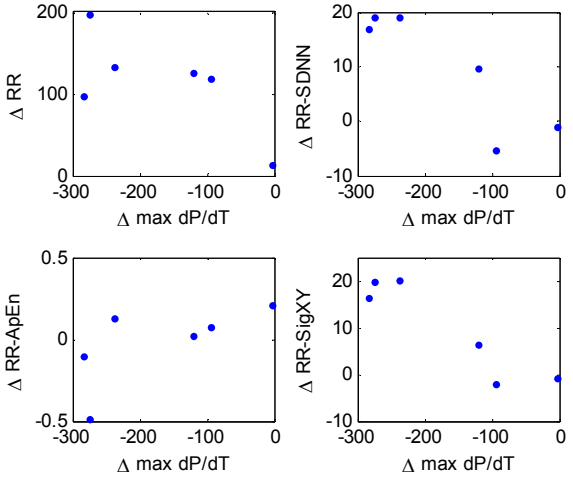

Figure 4: Changes in RR based variability metrics compared to changes in contractility (max dP/dT)

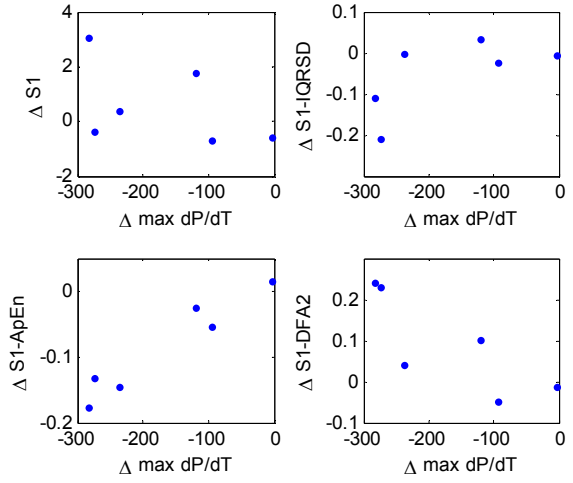

Figure 5: Changes in S1 based variability metrics compared to changes in contractility (max dP/dT)

A summary of all the relationships between changes in S1 interval based variability metrics and max dP/dT is shown in column 3 in Table 1. We found that while there was a mild correlation between the change in S1 amplitude based metrics and the change in max dP/dT, one of the nonlinear measures, the ApEn of the S1 amplitude, was highly correlated (r=0.96) with the change in contractility due to ischemia.

Metric (units when measured for RR interval)	Correlation Coefficient for change in HRV metric with change in max dP/dT	Correlation Coefficient for change in S1 metric with change in max dP/dT
Mean [msec]	-0.7066	-0.4705
Median [msec]	-0.6988	-0.512
SDNN [msec]	-0.8852†	0.0399
IQRNN [msec]	-0.973†	0.0608
CV [NA]	-0.8878†	-0.5298
SDSD [msec]	-0.4397	0.4271
IQRSD [msec]	-0.6182	0.6623
NIQRSD [msec]	-0.5876	-0.4077
RMSSD [msec]	-0.4931	0.5287
CVS [NA]	-0.4891	-0.4688
pNN50 [%]	-0.5736	-0.4563
HF [msec^2]	-0.5662	-0.5557
LF [msec^2]	-0.5806	-0.5552
Total Power [msec^2]	-0.5929	-0.5554
LF/HF [NA]	-0.4628	-0.511
HFW [msec^2]	-0.6029	-0.5789
LFW [msec^2]	-0.6962	-0.4653
LFW/HFW [NA]	-0.4795	-0.723
ApEn [regularity]	0.6802	0.9605†
SigXY [scatter]	-0.9224†	0.0852
FD [space filling]	-0.5554	0.1747
DFA1 [slope]	-0.8055	-0.457
DFA2 [slope]	-0.8412†	-0.8057†

Table 1: Correlation coefficients between the change in max dP/dT and change in different variability parameters for RR interval and S1 amplitude. Note that S1 amplitude has units in mG. †: p<0.05.

IV. Discussion

In this paper we evaluate the utility of multiple linear and non-linear variability metrics of RR interval and S1 amplitude for ischemia detection. We show that changes in HRV (SigXY) and S1 (ApEn) are highly correlated to changes in LV contractility, as measured by max dP/dT, during a balloon occlusion protocol. These findings may be related to changes in the autonomic tone during an ischemic event as a mechanism to compensate for the increased cardiac stress.

The main limitation of this study is the small number of animals. A correlation from 6 data points is encouraging and demonstrates minimal feasibility, but need to be validated by a larger data set. Drug interactions (such as phenylephrine, epinephrine and dobutamine) and anesthesia agents may have also influenced the results that we observed. In some animals, balloon catheter insertion took longer due to technical difficulties, which may influence the results due to pre-conditioning effect. As this observation is made from a swine ischemic model, this does not imply that similar changes will be seen in humans who may suffer a myocardial infarction. Although HRV and S1 amplitude have been shown to be correlated in an acute experiment, it is unclear whether the correlations would be consistent in an ambulatory setting.

This is the first time that the variability in S1 amplitude during cardiac injury has been studied. It is well known that the S1 amplitude is correlated to max dP/dT. Our novel findings related to the ApEn of S1 amplitude being correlated to changes in contractility during ischemia need to be further studied and examined in a larger clinical study.

V. Conclusion

The variability, as calculated by nonlinear methods, of signals from two noninvasive sensors, ECG and phonocardiogram, have been shown to be highly correlated to the changes of left ventricular pressure in a small, acute pre-clinical ischemia experiment.

VI. References

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