Detecting Suspected Pump Thrombosis in Left Ventricular Assist Devices via Acoustic Analysis

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Abstract*—*Objective: **Left ventricular assist devices (LVADs) fail in up to 10% of patients due to the development of pump thrombosis. Remote monitoring of patients with LVADs can enable early detection and, subsequently, treatment and prevention of pump thrombosis. We assessed whether acoustical signals measured on the chest of patients with LVADs, combined with machine learning algorithms, can be used for detecting pump thrombosis.** ***Methods:*** **13 centrifugal pump (HVAD) recipients were enrolled in the study. When hospitalized for suspected pump thrombosis, clinical data and acoustical recordings were obtained at admission, prior to and after administration of thrombolytic therapy, and every 24 hours until laboratory and pump parameters normalized. First, we selected the most important features among our feature set using LDH-based correlation analysis. Then using these features, we trained a logistic regression model and determined our decision threshold to differentiate between thrombosis and non-thrombosis episodes.** ***Results:*** **Accuracy, sensitivity and precision were calculated to be 88.9%, 90.9% and 83.3%, respectively. When tested on the post-thrombolysis data, our algorithm suggested possible pump abnormalities that were not identified by the reference pump power or biomarker abnormalities.** ***Significance:*** **We showed that the acoustical signatures of LVADs can be an index of mechanical deterioration and, when combined with machine learning algorithms, provide clinical decision support regarding the presence of pump thrombosis.**

Keywords*—*Left Ventricular Assist Device, Pump Thrombosis, Heart Failure, Machine Learning

I. Introduction

Pump thrombosis occurs in up to 10-13% of left ventricular assist device (LVAD) recipients within the first year post implant [1, 2]. Thromboembolic events may lead to pump failure requiring replacement at substantial rates (∼5-7%) which has been previously reported in large trials [3–5]. LVADs stimulate the coagulation cascade resulting in thrombus formation and, when exposed to the shearing force of blood flow, patients are predisposed to thromboembolic complications [6]. Pump thrombosis may result in hemodynamic derangement, stroke, and death [4, 6–8]. Presence of hemolysis [elevated plasma lactate dehydrogenase (LDH) or plasma free hemoglobin (pfHb) levels] and degradation of device performance (e.g., increased power) can indicate pump thrombosis, which is further investigated using echocardiogram ramp studies [9, 10].

Resultant end-organ dysfunction requires the exchange of the pump through an additional surgical procedure, which is expensive, and can contribute to higher allosensitization that is correlated with worse heart transplant graft survival outcome if associated with blood product use [11]. Moreover, device exchange does not preclude recurrence of thrombosis if the origin is biological rather than mechanical [7]. Therefore, device thrombosis should be mitigated with earlier diagnosis, before triggering any heart failure (HF) exacerbation and additional surgeries. In particular, outpatient monitoring is needed as up to 15% of patients are readmitted due to device thrombosis and subsequent complications increase healthcare costs and decrease patients' quality of life [12, 13]. Remote monitoring of pump parameters and hemodynamics should be achieved to allow real-time communication between caregivers and patients [14]. However, without having the required blood-derived biomarkers, it is not feasible to evaluate the normal vs. pathologic processes, or biological responses to therapeutic interventions. Nevertheless, such monitoring can be achieved by deriving "digital biomarkers" [15], which are measured through home-based sensors, wearable devices and implants, to support continuous measurement outside the physical confines of the clinic. Unfortunately, there is no technology currently available commercially nor in the research domain that has demonstrated the ability to characterize and monitor hemodynamics and pump functionality of VAD recipients at home.

In clinical settings, the operating sounds of these artificial blood pumps has been studied for assisting in thrombosis detection [16, 17]. Several studies, both in vitro [17–22] and in vivo [16, 17, 19, 21, 23–27], have evaluated acoustic analysis as a non-invasive method for thrombosis detection in axial and centrifugal pumps. These studies mostly leveraged harmonic frequency analysis and focused on detecting changes in the acoustic features following pump thrombosis. For example, Kaufmann et al. [16] asserted that the most intense harmonic is the fourth harmonic in the centrifugal pump recordings. Based on this assertion, they calculated the intensities of the first four harmonics and normalized the intensities of the first three to the fourth. They suggested that an increase in first and second harmonic intensities and the existence of the third harmonic indicate pump thrombosis. In addition, Yost et al. [19] and Castagna et al. [26] performed similar harmonic analysis on

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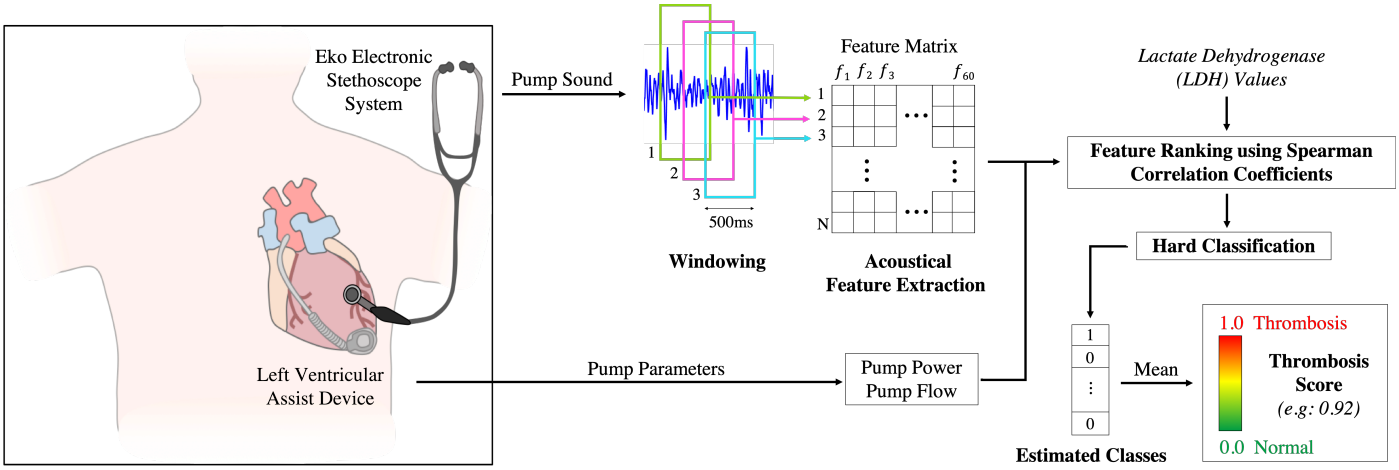

Fig. 1. System Overview. The digital stethoscope was placed on the patients exposed chest over the mitral valve and recordings were obtained in cases of changing pump speed or clinical condition. The acquired recordings were windowed and 60 acoustic features were extracted from each frame. Pump parameters (pump power and flow) were also added to the analysis. First, the top 15 most significant features were determined using LDH-based correlation analysis. We hypothesized that the features which have higher correlation with LDH values would perform better in thrombosis detection. After calculating the correlation coefficients for each LDH-feature pair, the selected features were fed to a logistic regression classifier which was validated using LOSO-CV. Each window was assigned an estimated class and the overall thrombosis score for any given recording was defined as the mean of these estimated values.

axial pump recipients. Yost et al. suggested that the normalized harmonic intensities decrease as the pump starts to develop thrombosis. On the other hand, Castagna et al. proposed that an increase in the normalized power of the first two harmonics and a decrease in the third harmonic indicate development of pump thrombosis.

To the best of our knowledge, no validated method has been reported so far. Moreover, the reliance on a single feature of pump acoustics - harmonic content - as an indicator of pump thrombosis may not be generalizable to all datasets and all pump types. In this work, we had two objectives: (1) determining salient acoustic and pump features indicative of pump thrombosis; and (2) evaluating the added value of acoustic features in thrombosis detection. Ultimately, this approach may enable detection and diagnosis of pump thrombosis with improved accuracy in clinical and/or home settings.

TABLE I. SUBJECT DEMOGRAPHICS, PUMP PARAMETERS AND BLOOD BIOMARKERS

SUBJECT DEMOGRAPHICS	
Age, y	57.4 ± 11.3
Male, %	84.6
Weight, kg	86.7 ± 20.1
Height, cm	179.1 ± 10.5
Number of Recordings per Subject	3.2 ± 4.2
BASELINE BLOOD AND PUMP MARKERS	
Speed, rpm	2738.8 ± 169.1
Flow, L/min	4.4 ± 1.0
Power, watts	4.6 ± 0.9
Pulsatility, L	3.5 ± 1.1
Systolic Blood Pressure, mmHg	98.4 ± 9.7
Diastolic Blood Pressure, mmHg	69.9 ± 7.6
Mean Arterial Pressure, mmHg	79.3 ± 7.4
Heart rate, bpm	79.2 ± 13.3
Hemoglobin, g/dL	12.1 ± 2.4
Hematocrit, %	36.0 ± 6.7
Partial Thromboplastin Time, sec	38.6 ± 15.0
INR	2.3 ± 0.7

II. METHODS

A. Study Protocol and Subject Demographics

This study was conducted under a protocol approved by the University of California San Francisco (UCSF) and Georgia Institute of Technology Institutional Review Boards and all patients provided written informed consent. Thirteen adult centrifugal pump recipients were enrolled in the study. At the time of enrollment - the first post-implant clinic visit when the patient was deemed clinically optimized - a baseline sound recording was obtained and baseline pump parameters and laboratory data were collected. All the LVAD patients implanted at UCSF are followed using a remote management system (Abbott Alere Home Monitoring, Livermore, CA or Acticare Health, Livermore, CA) that records daily pump parameters (speed, power, flow, pulsatility index, peak, trough, alarms), vital signs (blood pressure, heart rate, weight) and point of care CoaguCheck INR (Roche Diagnostics, Indianapolis, IN). In case of abnormalities in the pump parameters or HF symptoms, patients are contacted and hemolysis biomarkers (LDH, pfHb) are promptly obtained to establish the diagnosis of suspected pump thrombosis. During the study, new sound recordings were obtained in cases where there was a change in pump speed or clinical condition. All subjects were recipients of HeartWare HVAD (Medtronic Framingham, MA) device for either bridge-to-transplantation or destination therapy indications.

Patients were followed longitudinally for the outcome of suspected pump thrombosis, defined as abnormal pump parameters (power elevations above manufacturers baseline or an absolute power $\geq$ 10 Watts), hemolysis (LDH $>$ 500 IU/L, pfHb $>$ 20 mg/dL), development of unexplained HF or clinical hemolysis (hemoglobinuria), or poor left ventricular unloading during an echocardiographic ramp study. Due to the enhanced surveillance of the patients treated at UCSF, suspected pump

TABLE II. PUMP PARAMETERS AND BLOOD BIOMARKERS FOR BASELINE AND THROMBOSIS RECORDINGS

	Baseline (16 Recordings)	**Thrombosis (11 Recordings)**
Lactate Dehydrogenase (LDH), IU/L	291.4 ± 80.4	866.7 ± 382.9
Plasma Free Hemoglobin (pfHb), mg/dL	80%, <8 20%, 12.0 ± 5.6	50%, <8 50%, 133.4 ± 64.8
INR	2.2 ± 0.6	2.3 ± 0.8
Abnormal power by device manufacturer standards, %	N/A	81.8
Treatment with both tissue plasminogen activator and IV heparin, %	N/A	27.0
Treatment with IV heparin exclusively, %	N/A	54.5

TABLE III. NUMBER OF RECORDINGS FOR EACH SUBJECT

Sub. 1	1 baseline
Sub. 2	1 baseline, 3 thrombosis, 2 post-thrombolysis
Sub. 3	1 baseline
Sub. 4	3 baseline
Sub. 5	4 baseline, 3 thrombosis, 8 post-thrombolysis
Sub. 6	4 thrombosis, 3 post-thrombolysis
Sub. 7	1 baseline
Sub. 8	1 baseline
Sub. 9	1 thrombosis, 1 post-thrombolysis
Sub. 10	1 baseline
Sub. 11	1 baseline
Sub. 12	1 baseline
Sub. 13	1 baseline
TOTAL	41 recordings (16 baseline, 11 thrombosis, 14 post-thrombolysis)

thrombosis was determined based on abnormal pump parameters and hemolysis. In patients hospitalized for suspected pump thrombosis, clinical data and sound recordings were obtained at admission, prior to and after administration of thrombolytic or anticoagulation therapy, and every 24 hours until laboratory and pump parameters normalized. Thrombus resolution was defined as normalization of pump power and LDH with no clinical evidence of hemolysis for at least 24 hours.

B. Study Design and Data Acquisition

All sounds during the study period were collected and stored using the Eko Electronic Stethoscope System (Eko Devices, Inc. Berkeley, CA). With the patient in the supine position in a quiet room, the diaphragm of the stethoscope was placed on the patients exposed chest over the mitral valve for 15 seconds (Figure 1). The stethoscope settings were as follows: 40x gain, 4kHz sampling rate, 20Hz - 2kHz bandwidth.

Each recording was assigned to one of three groups for analysis: 'normal' for the baseline recording obtained at enrollment, 'thrombosis' for recordings obtained when a patient met the above criteria for suspected thrombosis, and 'post-thrombosis' for recordings obtained after initiation of medical treatment until normalization of pump parameters. For the post-thrombosis analysis, we used the recordings which were taken when the pump parameters and biomarkers returned to normal. The procedure by which recordings were processed and analyzed was as follows: (1) windowing and feature extraction; (2) feature selection using correlation analysis, (3) threshold selection and thrombosis score calculation.

TABLE IV. FEATURE DESCRIPTIONS OF DIFFERENT FEATURE GROUPS

Feature Group	**Features**
Temporal	Zero Crossing Rate (ZCR), Energy, Energy Entropy
Spectral	Spectral Centroid, Spectral Spread, Spectral Flux, Spectral Entropy and Spectral Roll-off
MFCC	13 Mel-frequency Cepstrum Coefficients
Bandpower	Signal power in 29 distinct frequency bands, between 30 logarithmically spaced frequencies in the range of 20Hz - 2kHz.
Wavelet	3-level Daubechies8 wavelet transform was computed and the bandpower of the 3rd level approximation and detail coefficients and 2nd level detail coefficients were calculated. [28]
Non-linearity	Fundamental frequency, total harmonic distortion (odd harmonics), total harmonic distortion (even harmonics)
Harmonic	First, second, third and fourth harmonic amplitudes

C. Pre-processing and Feature Extraction

In this study, we had 41 recordings from 13 subjects (16 normal (baseline), 11 thrombosis and 14 post-thrombolysis). The average number of days post-implantation the recordings were obtained was 372, ranging between 11 and 1374. Information about subject demographics, pump parameters and blood biomarkers can be found in Tables I and II. Detailed information about the recording types is presented in Table III. In this paper, we focused on generalization across recordings rather than generalization across subjects as it is more important to demonstrate whether the method is consistent regardless of when the recording is performed for a particular patient. Thus, the signals were segmented into 500 ms frames with 90% overlap to increase the number of instances. From each frame, we extracted 60 acoustic features. In the recent studies, the best indicators for detecting various pump states were shown to be the spectral content of the signals, as these pump states may have different frequency characteristics [16, 19, 29]. Contrarily, we hypothesized that having a more diverse feature set would enhance the classifier performance, thus we explored various different features. Our feature set included the common audio-processing features [28, 30] and features used in previous LVAD studies [16, 19, 26]. We categorized our features as 'temporal', 'spectral', 'MFCC', 'bandpower', 'wavelet', 'non-linearity' or 'harmonic' features. Detailed information about these features can be found in Table IV. Extracted features were stored in a matrix, where each row represents a single frame and the columns represent the 60 features extracted. In addition to our 60 acoustical features, we also tested the reference pump parameters (pump power and pump flow) as our features, which resulted in 62 features in total (Figure 1).

D. Feature Selection using Spearman Correlation Analysis

In the previous section, we presented the features we extracted; however as in many other cases, these features are selected ad hoc with a black box approach. Therefore, we eliminated the redundant features while keeping the informative ones; because although having more features can give extra power to ML algorithms, focusing on the intrinsic dimension is usually more desirable for preventing overfitting and ensuring robustness [31–33]. In addition, a mapping between

blood-derived biomarkers and acoustical features should be quantified for evaluating the pathological processes or tracking therapeutic interventions accurately outside of the clinic, as the ideal scenario is recording and analyzing the pump sounds of the subjects outside the clinic in the absence of blood tests or any additional diagnostic tool. Based on this motivation, we hypothesized that finding the features which are highly correlated with the blood biomarkers may help us to exclude the redundant features and include the most related ones to construct a global feature set, which can be used for all subjects in thrombosis detection without any need for blood work [34].

As previously discussed, changes in hemolysis biomarker values (LDH $>$ 500 IU/L, pfHb $>$ 20 mg/dL) indicate pump thrombosis, therefore we hypothesized that if we could determine the acoustical features which have similar trends with the hemolysis biomarkers, our classifier might have a higher performance in thrombosis detection. For this study, we preferred LDH values over pfHb values as our reference, since it would not be possible to use some of the pfHb values (such as pfHb $<$ 8 as in Table II). Also, recent studies proposed LDH as the primary [4, 35–37] and the most specific indicator [38, 39] of thrombosis in LVADs.

We used Spearman correlation analysis [40] to investigate the relationship between the LDH values and our acoustical features. We chose Spearman correlation instead of Pearson correlation as it does not make any assumptions regarding the frequency distribution of the variables or does not require a linear relationship between them. We wanted to treat our features as independent agents, because although some features (such as harmonics) are based on the same fundamental frequency, their behavior may be different during thrombosis development and there is no consensus across different studies [16, 19, 26]. We calculated the Spearman correlation coefficient ρ for each LDH - feature pair (e.g.: LDH and ZCR, LDH and Energy, etc.) which resulted in 62 correlation coefficients varying between -1 and 1. We then took the absolute value of these correlation values and ranked them in descending order. We determined 0.3 as our cut-off correlation coefficient as any value below 0.3 is considered negligible in the literature, especially in medical research [41–43]. Thus, we decided to use the features which have absolute correlation coefficient above 0.3 (when rounded to two significant digits). Based on this investigation, we included 15 features in our final feature set. Note that the target labels of the normal and thrombosis groups were not included in this investigation, so the analysis was not biased.

After ranking the features based on their correlation with LDH values, we plotted the kernel density estimate (KDE) plots for the best and worst performing features to visualize the differences in their probability density functions [44]. We expected to see distinguishable density functions between normal and thrombosis classes if a feature has high correlation with LDH biomarker. After determining our top 15 features, we continued with threshold selection and thrombosis score calculation.

E. Threshold Selection and Thrombosis Score Calculation

We determined our end goal as deriving a thrombosis score to place the recordings on a scale ranging from 0 (normal) to 1 (thrombosis). To calculate the thrombosis score, we trained our classifier twice: using *top 15 features* and *all 62 features*, to test the effectiveness of our correlation-based feature ranking. The classifier was validated using leave-one subject-out cross-validation (LOSO-CV). In each cross-validation fold, all recordings from one subject were left out and the logistic regression classifier was trained using the recordings from the remaining subjects. The model was then tested on the recordings from the subject being left out. This procedure was completed for all subjects. Note that the post-thrombosis data was not used for training, as the ground truth labels for this data were not known certainly - in many cases, thrombosis can be recurrent even following treatment.

Logistic regression was our preferred method due to several reasons. First, it is easy to implement and interpret - for example it does not require heavy scaling or tuning. This was our primary motivation, as an application like thrombosis detection is a collaborative work between medical doctors, researchers and patients; therefore, comprehensibility is an important consideration. Secondly, it is widely used in biostatistical applications where binary responses occur quite frequently, such as patients having heart disease or not, etc. [44]. Therefore for a case like thrombosis detection, it is well suited.

In more detail, let R denote our training data. Each instance within our training set corresponds to a 500ms-long frame in the form $(\mathbf{x}_i, y_i)$, where $\mathbf{x}_i = (x_{i,1}, x_{i,2}, ..., x_{i,62})$ are our 62 features, and y_i is our thrombosis label (0 or 1). The training dataset R is used to build our logistic regression classifier $\mathcal{M}$ which predicts the class of an incoming frame using its features. i.e., $\mathcal{M} : \mathbf{x} \rightarrow$ *predicted thrombosis label*. In each fold, R includes data from all subjects, except the subject whose recordings are being tested. At prediction time, 302 unlabeled frames from each recording are provided to $\mathcal{M}$, and $\mathcal{M}$ predicts their labels as 0 or 1 (hard classification). This prediction phase was completed for all recordings of the subject which had been left out in the training phase. In the following folds, the same pipeline was followed for all subjects. We define the **thrombosis score** of each recording as the mean of the predicted classes of all 302 frames within that recording.

Using the thrombosis scores we obtained from LOSO-CV and the actual class labels, we plotted the receiver operating characteristic (ROC) curve to investigate how our two models (with 15 features and with all features) behave for different threshold values. After showing the superior performance of our condensed feature set, we determined the best threshold value for our application using the ROC curve we plotted. Since ROC represents the probability of detection (true positive rate) vs. probability of false alarm (false positive rate) for different threshold values, we selected a threshold which maximizes the probability of thrombosis detection while minimizing the probability of false alarm. We therefore selected the optimum threshold for our classification problem, which helped us to discard the sub-optimal models. The generalizability of the classifier was then assessed by calculating the accuracy, sensitivity, and precision values based on the threshold we selected. In the final part of the

scoring procedure, the constructed model using the baseline and thrombosis recordings was fit into the post-thrombolysis data to investigate the pump conditions after heparin and/or tissue plasminogen activator (tPA) treatments.

F. Performance Comparison with Existing State-of-the-Art Methods

To benchmark the performance of our approach - which integrates multiple acoustic features using machine learning approaches rather than focusing on one or two individual features - we employed the reference parameters (pump features obtained from the controller) and state-of-the-art algorithms from the existing literature and compared the results of these approaches to our method. First, the classification was performed using the reference parameters: only the pump power and only the pump flow values as our features. As these parameters are directly associated with abnormal pump functionality, the performance metrics of these reference variables and our proposed method were compared.

Second, Kaufmann et al. [16] asserted that the most intense harmonic is the fourth harmonic in centrifugal pumps; therefore based on their methods, we calculated the intensities of the first four harmonics for each recording. They suggested that an increase in the first and second normalized harmonic intensity and the existence of the third harmonic suggest pump thrombosis. We investigated the effectiveness of their features both with and without a machine learning approach - first we compared the values of the harmonic intensities for normal and thrombosis recordings, then we reported the classifier performance which was trained using only these normalized intensities as features.

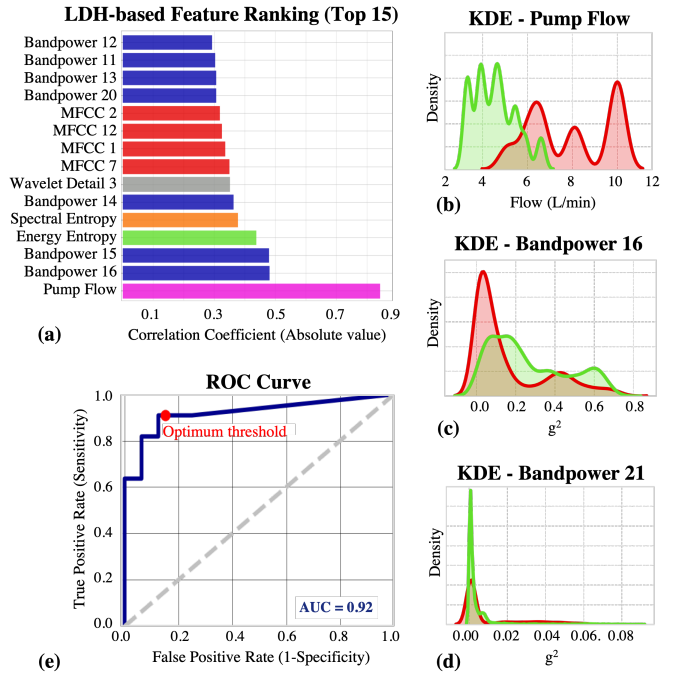

Fig. 2. Results. (a) The 15 features having the highest absolute correlation with LDH are presented. There is a great diversity in the feature types, thus each feature group has a relationship with the LDH values. (b) KDE plot for the most correlated feature, pump flow. (c) KDE plot for the most correlated acoustic feature, bandpower 16 (190 - 230 Hz band). (d) KDE plot for the least correlated feature, bandpower 21 (440 - 520 Hz band). (e) ROC curve when the classifier was trained using the top 15 features. The are under the curve (AUC) was calculated to be 0.92. The decision threshold was determined to be 0.15 as it is the optimum value for maximizing the TPR ($\sim$ 0.91) while minimizing the FPR ($\sim$ 0.13).

III. Results and Discussion

A. Feature Selection using Spearman Correlation Analysis

As explained in Section II-D, we calculated the Spearman correlation coefficient for each LDH-feature pair and used these correlation values as our feature ranking metric. Our hypothesis was that the features which have higher correlation with LDH values would perform better in thrombosis detection. Also, we wanted to eliminate the redundant features for the sake of robustness and simplicity. The 15 features having the highest absolute correlation coefficient are reported in Figure 2(a). Each color represents a different feature group (e.g.: green: temporal, orange: spectral, etc.) As seen in the bar graph, there is a great diversity in the colors, thus each feature group has a relationship with the LDH values. Also highly correlated features do not come from a single group, which makes the investigation of a diverse feature set rather that relying solely on one feature group (like harmonics) even more desirable.

To test whether the highly correlated features are indeed better in distinguishing between normal and thrombosis groups, we plotted the KDE plots and observed the differences in distributions (Figure 2(b-d)). We plotted the distributions of the top feature (pump flow, ρ=0.84), the top acoustical feature (bandpower 16, $\sim$ 195-230 Hz, ρ=0.48) and the least correlated feature (bandpower 21, $\sim$ 440-520 Hz, ρ=0.012). In the graphs, we colored the thrombosis recordings with red and normal recordings with green. If a specific feature has the ability to distinguish between two groups, we expected to see less overlapping distributions. As expected, it is visually clear that the features having higher correlations with LDH have less overlapping distributions compared to the ones having lower correlation. Thus, we justified that if a feature behaves similar to the actual blood biomarker, it will be more significant in thrombosis detection; therefore a mapping between our "acoustical biomarkers" and actual "blood biomarkers" is indeed achievable.

B. Threshold Selection and Thrombosis Score Calculation

As explained in Section II-E, we ran our algorithm twice: 1) Using *the top 15 features*, 2) Using *all 62 features*. We plotted the ROC curves for both experiments to investigate whether our correlation-based feature selection algorithm helps to increase classifier performance and eliminate the redundant features independent of the threshold we would use. When all 62 features were used, the area under the ROC curve was calculated to be 0.764, whereas for the top 15 features, this value was 0.921. This justified that the Spearman correlation coefficients between the features and LDH values can be

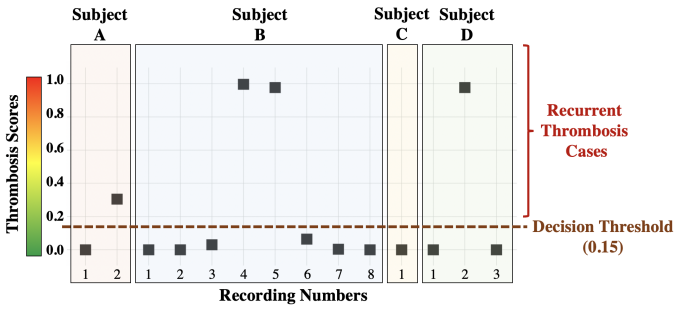

Fig. 3. The constructed model using the baseline and thrombosis recordings was fit into the 14 post-thrombolysis recordings taken from 4 subjects to investigate the pump conditions after treatment. The results revealed that, while pump power and hemolysis biomarkers may indicate that the thrombosis is resolved, there may still be other problems such as altered pump mechanics, increased friction, or even residual pump thrombosis that cannot be identified by these markers. Indeed, recurrent thrombosis episodes were observed in 3 of the 4 subjects following the treatment of thrombosis, and the 4 recordings which had scores above the threshold belonged to these 3 subjects.

used to rank and select the most prominent features. Also, another important point is that having more features is not always beneficial for the model and redundant features should be eliminated. A similar approach can be applied to many other biosignals to focus on the most relevant features while eliminating the unnecessary and deviating ones for a more robust analysis. Based on the ROC curve we plotted using our 15 features in Figure 2(e), we determined our threshold as 0.15 as it was the best value which maximizes the TPR (probability of detection) while minimizing the FPR (probability of false alarm). Using this threshold, we calculated our accuracy, sensitivity and precision to be 88.9%, 90.9% and 83.3%, respectively.

Additionally, the constructed model using the baseline and thrombosis recordings was fit into the post-thrombolysis data to investigate the pump conditions after heparin and/or tPA treatments. The model was tested on 14 post-thrombolysis recordings taken from 4 HVAD subjects; however, although the pump parameters and hemolysis biomarkers returned to normal, the scores were varying from 0 to 1, rather than being closer to 0, with 4 of the 14 recordings being above the thrombosis threshold and 10 being below the threshold (Figure 3).

The results from the post-thrombolysis recordings from 4 subjects revealed that, while pump power and hemolysis biomarkers may indicate that the thrombosis is resolved, there may still be other problems such as altered pump mechanics, increased friction, or even residual pump thrombosis that cannot be identified by these markers. Indeed, for 3 of the 4 subjects, recurrent thrombosis episodes were observed following the treatment of thrombosis, and the 4 recordings which had scores above the threshold belonged to these 3 subjects (Subjects A, B, D in Figure 3). We further investigated the clinical logs of these 3 subjects, and found out that the subjects had indeed been diagnosed with recurrent thrombosis right after the recordings having higher scores. The ability to predict recurrent thrombosis by supplementing pump power and blood biomarker data with acoustical signatures measured from the pump should be evaluated extensively in future studies. Note that no direct confirmation of pump thrombosis was available in the study as no devices were exchanged.

TABLE V. PERFORMANCE COMPARISON WITH STATE-OF-THE-ART METHODS

	Accuracy	Sensitivity	Precision
Pump power	62.9 %	27.3 %	60.0 %
Pump flow	81.4 %	72.7 %	80.0 %
Harmonic analysis (Kaufman et al.)[16]	74.1 %	63.6 %	70.0 %
Our method	**88.9 %**	**90.9%**	**83.3 %**

Pump thrombosis decision is currently based on the presence of hemolysis and degradation of device performance, which is further investigated using echocardiogram ramp studies [9, 10]. In these studies, left ventricle end-diastolic diameter is monitored in response to changing LVAD speed, which may potentially diagnose pump thrombosis or other obstructions within the pump [45]. However, there is a need for a convenient remote monitoring system for LVAD recipients for early detection of thrombus formation, therefore patients should be able to monitor their LVAD status at home continuously. In particular, the patients at home could use the microphone function of their smartphones and transmit these sounds electronically to the cloud for analysis. Machine learning algorithms could then be employed to identify abnormal recordings from baseline, initiating a warning for patients and caregivers before thrombosis exacerbation and determining the need for clinical pump or blood tests. This way, early diagnosis and optimum treatment recommendations could be achieved, and this could help preventing HF aggravation and additional surgeries.

C. Performance Comparison with Existing State-of-the-Art Methods

Using only pump power values, accuracy, sensitivity and precision values were 62.9%, 27.3% and 60.0%, respectively. Using only pump flow values, the corresponding values were 81.4%, 72.7% and 80.0%. This demonstrates that mechanical power or blood flow characteristics are not sensitive nor specific enough to detect the suspected pump thrombosis episodes by themselves. On the other hand, flow showed higher performance in thrombosis detection compared to power probably due to frequently adapted hematocrit settings, which affected the flow calculation but not power consumption. Thus, we can say that although one of the most prominent clinical signs for thrombosis development is elevated pump power, the combination of acoustic features and pump flow values yields higher thrombosis detection rate and accuracy as we showed in Table V.

Furthermore, when we applied the approach outlined by Kaufmann et al. [16] on our dataset, the fourth harmonic was the most intense harmonic in only 17 of 41 recordings. Nevertheless, we normalized the first, second and third harmonic intensities to the fourth harmonic intensity as the authors explained. We found the average intensity for the normalized first harmonic to be 2.46 ± 3.52 and 3.06 ± 2.43 for the control and thrombosis groups, respectively. For the second harmonic, these values were 0.43 ± 0.57 and 2.01 ± 2.70 for the control

and thrombosis groups, respectively. Indeed, these intensities increase as the pump starts to develop thrombosis as seen in previous work; however, high inter-recording variability resulted in lower than expected performance for classifying thrombosis. As the next step, we evaluated our model using the harmonic features and reported all classification results in Table V. However, it is important to note that Kaufmann et al. averaged 30 spectra in their work, whereas we are computing harmonics from single 500 ms frames, which is likely noisier. Thus, this should not be considered as a direct comparison.

D. Limitations and Future Work

Currently, there is no clinical gold standard existing for certain comparisons. Therefore, the findings in this work may serve as the preliminary evidence for developing an extensive clinical study in the future. This study was limited by a relatively small sample size, and the study was conducted at a single clinical site; accordingly, future studies will be needed to assess the reproducibility of the methods. Moreover, as the number of subjects in the training set is increased, the generalizability and prospective validation of our algorithm will be improved as will the determination of key acoustical features associated with pump thrombosis. In addition, although our proposed algorithm may eventually help to decrease the frequency of hospital visits and blood tests, recording the sound signals and processing them requires additional time and computational power, compared to bedside testing.

While our current work leverages hard classification using logistic regression due to their high interpretability in the medical domain, we plan to investigate the integration of soft-classification algorithms and calibration curve implementation into our study in future work. Similarly, the effect of recording length on feature sensitivity (e.g. sensitivity to harmonics) should be investigated in future studies. In this work, we calculated the bandpower features within fixed frequency bands. In future work, we will investigate the possibility of obtaining higher accuracy if the frequency bands were adapted based on the pump speed. Lastly, we used LDH as the reference blood-biomarker to employ correlation-based feature ranking and excluded any other condition that may have increased LDH. In our future studies, we will investigate the correlation between the acoustic features and other blood-biomarkers as well.

IV. Conclusion

We demonstrated that the acoustical signatures of LVADs, combined with machine learning algorithms, can improve the detection accuracy of suspected thrombosis outcomes. Additionally, the scoring of post-thrombolysis recordings suggested residual pump thrombosis which is not identified by pump parameters or hemolysis markers. Additionally, patients who have normal pump operations but abnormal levels of hemolysis markers could benefit from acoustic analysis to detect acoustic signs consistent with thrombosis. As there is a need for a convenient remote monitoring system for VAD recipients, patients should be able to monitor their VAD status at home. Once our algorithm is evaluated prospectively and demonstrates improvement in clinical management of pump thrombosis, the use of acoustical patterns can potentially enable detection of suspected pump thrombosis when biomarkers and pump parameters are non-diagnostic.

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