Estimating Left Ventricle Ejection Fraction Levels Using Circadian Heart Rate Variability Features and Support Vector Regression Models

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Abstract*—*Objectives: **The purpose of this study was to set an optimal fit of the estimated LVEF at hourly intervals from 24-hour ECG recordings and compare it with the fit based on two gold-standard guidelines.** ***Methods:*** **Support vector regression (SVR) models were applied to estimate LVEF from ECG derived heart rate variability (HRV) data in one-hour intervals from 24-hour ECG recordings of patients with either preserved, mid-range, or reduced LVEF, obtained from the Intercity Digital ECG Alliance (IDEAL) study. A step-wise feature selection approach was used to ensure the best possible estimations of LVEF levels.** ***Results:*** **The experimental results have shown that the lowest Root Mean Square Error (RMSE) between the original and estimated LVEF levels was during 3–4 am, 5–6 am and 6–7 pm.** ***Conclusion:*** **The observations suggest these hours as possible times for intervention and optimal treatment outcomes. In addition, LVEF classifications following the ACCF/AHA guidelines leads to a more accurate assessment of mid-range LVEF.** ***Significance:*** **This study paves the way to explore the use of HRV features in the prediction of LVEF percentages as an indicator of disease progression, which may lead to an automated classification process for CAD patients.**

***Index Terms*—Heart failure (HF), left ventricle ejection fraction (LVEF), coronary artery disease (CAD), electrocardiography (ECG), heart rate variability (HRV), machine learning, support vector regression (SVR).**

Manuscript received March 15, 2020; revised May 15, 2020; accepted June 8, 2020. Date of publication June 15, 2020; date of current version March 5, 2021. This work was supported in part by (award number 8474000132), in part by Healthcare Engineering Innovation Center (HEIC) at Khalifa University Abu Dhabi, UAE, and in part by ADEK (award number 29934,2018). *(Corresponding author: Ahsan Khandoker.)*

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Digital Object Identifier 10.1109/JBHI.2020.3002336

I. Introduction

HEART Failure (HF) is a life-threatening disease defined as the inability of the heart to pump enough blood through the body to meet physiological demand. According to the European Society of Cardiology (ESC), more than 26 million people worldwide are suffering from HF with an approximate 17–45% mortality rate within the first year of admission [1]. Based on the report of the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA), HF is classified into four stages, i.e., Pre-HF, Asymptomatic-HF, Symptomatic-HF, and Advanced-HF. There are many factors that contribute to the classification of HF, such as fatigue, weight gain, and shortness of breath. The major cause of HF is coronary artery disease (CAD), followed by hypertension, diabetes, valvular heart disease and cardiomyopathy [2], [3]. To diagnose HF patients, the integration of patient history, physical examination, and clinical tests is important [4], in addition to the Left Ventricle Ejection Fraction (LVEF), which is the most common indicator of the extent of heart failure [5], [6]

LVEF is the percentage of blood leaving the left ventricle at each beat and determined from the ratio between the stroke volume and the end-diastolic volume [4]. The current ACCF and AHA guidelines [7] classify HF with respect to LVEF into three stages: (a) HF with preserved EF (pEF, EF$>50\%$), (b) HF with reduced EF (rEF, EF$<40\%$), and (c) HF with mid-range EF (mEF, $40\% \leq$ EF$\leq 50\%$). In patients with pEF, the dysfunction of the heart mainly occurs in the diastolic phase, where the muscle of the heart becomes stiff and does not relax between contractions and does not completely fill the ventricle. This accounts for approximately more than half of the HF patient population, with the majority of patients being elderly females. On the other hand, patients with a rEF present with systolic dysfunction, in which the left ventricle does not eject enough blood to the body due to weakness of the cardiac muscle [4], [8]. In patients with mEF, the amount of blood pumped out of the heart with each beat is close to the pEF, primarily due to atrial enlargement and left ventricular hypertrophy (LVH) of the heart.

LVEF can be estimated from, cardiac catheterization [9], [10], computerized tomography (CT) [11], and nuclear medicine scans [12]. However, the gold standard and the most commonly used techniques for measuring LVEF are echocardiography and

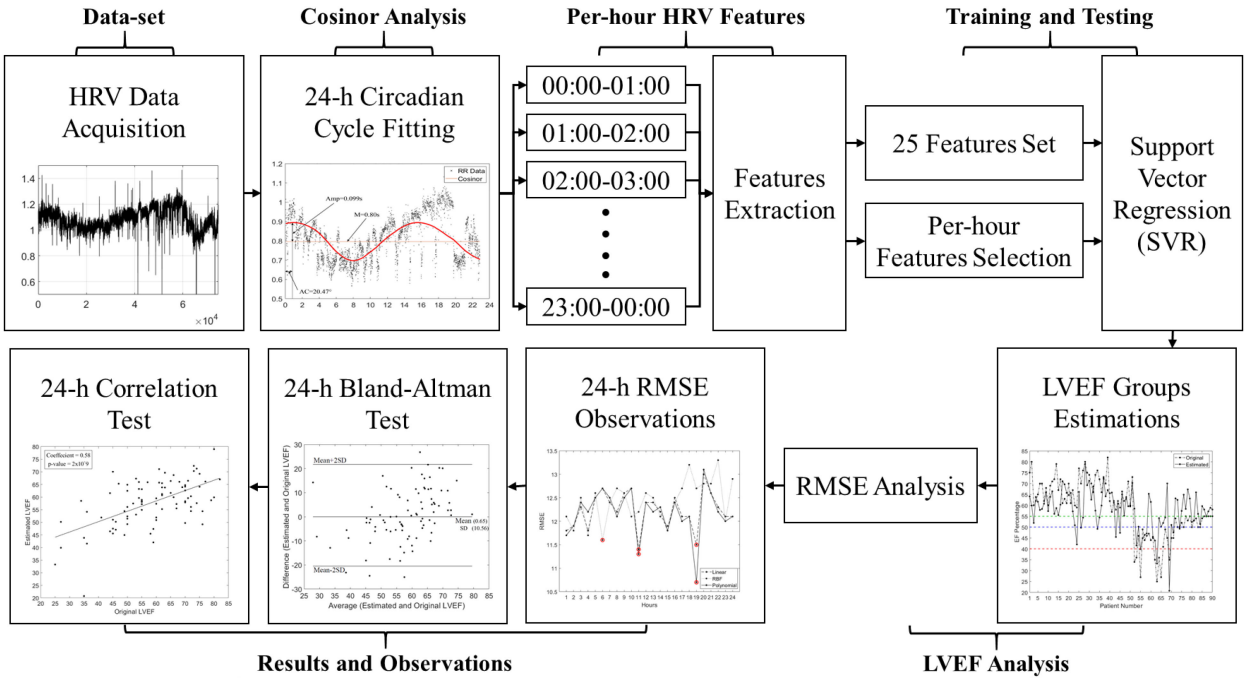


Fig. 1. An illustration of the overall procedure followed in this study.

cardiovascular magnetic resonance (CMR) imaging [13]–[15]. Despite the advantages of these techniques, including the high accuracy (LVEF estimation error <4%) [16] and the use of non-ionizing radiations, they may lead to complications and are relatively expensive as a public health service [10]. Therefore, electrocardiography (ECG) presents an alternative, inexpensive and widely available tool to diagnose LVEF [17]. Determination of heart failure and its progression from ECG recordings, that can indicate left ventricular hypertrophy (LVH), left bundle branch block (LBBB) and atrial fibrillation (AF), has limitations with false-positive rates being substantial [18]. An alternative is to apply Heart Rate Variability (HRV) analysis for detection of HF utilising data-mining techniques

A. Research Questions

HRV and its corresponding features have been commonly used in the diagnosis of cardiovascular diseases. Most research has focused on determining risk or the recognition of abnormal HRV patterns in patients with congestive heart failure, paroxysmal atrial fibrillation, and arrhythmia including cardiac autonomic neuropathy [19]–[22]. In most of these studies, the automated HRV classification was applied to quantify the mortality rate or to identify patients that are more prone to cardiac death [23]–[25]. Despite achieving high levels of accuracy in automated classification for such applications, predicting levels of LVEF from HRV data is less well studied in the literature and, especially, circadian rhythm with respect to heart failure progression and treatment optimisation by consideration of circadian variation [26]. Determining a clinically useful association between LVEF and HRV is hampered by the lack of an optimal cutoff-point for mid-range EF. Several studies have shown an increased risk of HF and mortality in asymptomatic patients with an mEF of 40% to 50% compared to patients with mEF of 50% to 55% [27], [28]. Similarly, the Multi-Ethnic Study of Atherosclerosis (MESA) reported that a 12-fold increased risk of HF was linked to a decrease in LVEF to $< 50\%$ [29], [30]. However, the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) set the normal EF at $> 55\%$ [31]. Therefore, the question arises whether there are any pathophysiological differences associated with the two classification systems and, if so, how does this influence HRV.

B. Contribution

Motivated by the aforementioned, an estimation of the LVEF levels of CAD patients is proposed here by using hourly HRV data over a 24-hour period. The novelty of the proposed approach lies in using a simple, yet effective, machine learning technique to fit HRV data and provide corresponding estimations of LVEF levels. ECG is a noninvasive test that allows the determination of HRV based on the analysis of a 24-h heart rate recording, which has not been examined so far. Unlike the current gold standards, the use of ECG recordings combined with HRV is a promising alternative for frequent testing of CAD progression. In addition, the proposed study explores the circadian rhythm of HRV data and points out critical window hours that are most prominent in discriminating the three LVEF categories. Thus, knowledge of the best HRV features that discriminate the LVEF-based HF categories combined with a one-hour recording at the specified time can be used as a noninvasive technique for determining LVEF at that time interval and whether further tests are required (Fig. 1).

TABLE I
DEMOGRAPHIC INFORMATION UNDER THE TWO MID-RANGE EF CLASSIFICATION SCHEMES

	LVEF Classification 1			LVEF Classification 2			Overall
	Preserved	*Mid-range*	*Reduced*	*Preserved*	*Mid-range*	*Reduced*	
Patients (n)	51	20	21	65	19	8	**92**
Gender (M/F)	44/7	19/1	21/0	57/8	19/0	8/0	**84/8**
Age (yrs)	35-79	40-84	40-80	35-84	40-80	41-70	**35-84**
(Mean±Std)	(55.98±11.11)	(58.68±11.57)	(57.00±11.15)	(56.42±11.27)	(59.22±11.42)	(54.25±9.74)	**(56.79±11.14)**
BMI	19.72-36.33	17.99-33.96	21.55-36.85	17.99-36.33	22.55-31.26	21.55-36.85	**17.99-36.85**
BP (Systolic/Diastolic)	100-160/60-90	100-140/50-90	90-150/60-95	100-160/50-90	90-150/60-95	90-130/60-80	**90-160/50-95**
LVDS (mm)	22-55	26-45	31-66	22-55	31-57	33-66	**22-66**
(Mean±Std)	(33.37±6.78)	(37.23±4.48)	(44.56±9.03)	(33.87±7.53)	(42.14±7.52)	(46.21±12.73)	**(36.80±9.24)**
LVDD (mm)	33-59	40-68	28-75	33-68	37-71	28-75	**28-75**
(Mean±Std)	(50.53±4.98)	(54.08±7.03)	(55.02±11.79)	(51.02±6.49)	(54.72±10.91)	(55.71±16.32)	**(52.21±8.84)**
Smoking (Yes/No)	40/11	13/7	19/2	50-15	14/5	7/1	**71/21**
Syncope (n)	3	5	1	7	1	1	**9**
VT (n)	6	0	5	5	2	4	**11**
Medications (*Beta-Blockers, Digoxin, Diuretic, ACE Inhibitor, Anti-Arrhythmics*)							
Beta-Blockers (Yes/No)	36/15	12/8	13/8	42/23	15/4	4/4	**61/31**
Digoxin (Yes/No)	0/51	0/20	0/21	0/65	0/19	0/8	**0/92**
Diuretic (Yes/No)	0/51	0/20	3/18	0/65	1/18	2/6	**3/89**
ACE Inhibitor (Yes/No)	6/45	3/17	3/18	8/57	2/17	2/6	**12/80**
Anti-Arrhythmics (Yes/No)	3/48	2/18	3/18	4/61	2/17	2/6	**8/84**

BMI: Body Mass Index, BP: Blood Pressure, LVDS: Left Ventricle Systolic Dimension, LVDD: Left Ventricle Diastolic Dimensions, VT: Ventricle Tachycardia, ACE: Angiotensin-converting enzyme.

II. MATERIALS AND METHODS

A. Data-Set

The data set was obtained from the Intercity Digital ECG Alliance (IDEAL) study of the University of Rochester Medical Center Telemetric and Holter ECG Warehouse (THEW) archives [32]. The study covered 271 patients with CAD, who had at least one vessel narrowing $> 75\%$ and a positive angiogram. All patients had either an exercise induced ischemia or a record of a myocardial infarction. Patients were in sinus rhythm with stable conditions of ischemic heart disease prior to the study, in agreement with the enrollment criteria of patients being only eligible two months following any cardiac event. The patients included in the study were free of (exclusion criteria):

- dilated cardiomyopathy,
- unstable coronary condition (Unstable angina),
- congestive heart failure (CHF),
- previous coronary artery bypass surgery (CABG),
- not in sinus rhythm including atrial flutter/fibrillation, pacemaker rhythm, and AV block,
- renal or cerebral vascular disease and severe haptic disease.

All patients eligible for the study had an echocardiography test to estimate their LVEF level followed by a Holter 24 hour ECG using a three pseudo-orthogonal lead configuration. The ECG recording started with a 20 minute rest period in a supine position prior to commencing the ambulatory recording.

The final data-set included 92 patients (84 M/8F) following exclusions and removing 110 patients with hypertension, 9 with diabetes and 27 with hypertension and diabetes. Furthermore, the original data-set included 33 patients with missing LVEF measurements or missing annotations. All patients were classified according to the mid-range EF group classification system mentioned in Section I as follows:

- **LVEF Classification 1:** pEF (EF$>$ 55%), mEF (50% $\leq$ EF $\leq$ 55 %), and rEF (EF $<$ 50%) [31].
- **LVEF Classification 2:** pEF (EF$>$ 50%), mEF (40% $\leq$ EF $\leq$ 50%), and (rEF$<$ 40%) [7].

The complete demographic information of patients included in this study is shown in Table I.

B. Cosinor Analysis

Initially, the RR interval data were manually reviewed, and any ectopic beats and/or noise removed, providing biosignals of normal beats (NN intervals). Then, the annotated NN interval data were fitted by a Single Cosinor Analysis fitting algorithm [33]. From the Cosinor fitted data, the Midline Estimating Statistic of Rhythm (MESOR-M), which is a measure of the average value of the fitting curve, the Amplitude (Amp), which is half the height of oscillations within the fitting curve, and the Acrophase (AC), which measures the occurrence of a peak within the rhythm fitting curve, were determined [33]–[35]. For the Cosinor analysis, the reference angle was set at 0°, and for each clock hour, the resulting acrophase was converted into a 24-h angle, using (360/24), resulting in a 15° phase per hour. Fig. 2 shows an example of a selected patient with NN interval data along with the Cosinor analysis fitting. The observed acrophase (35.14°) was then converted to the starting hour, set at 2 am. After obtaining the starting hour, the 24-h data sequence was fixed to start from midnight.

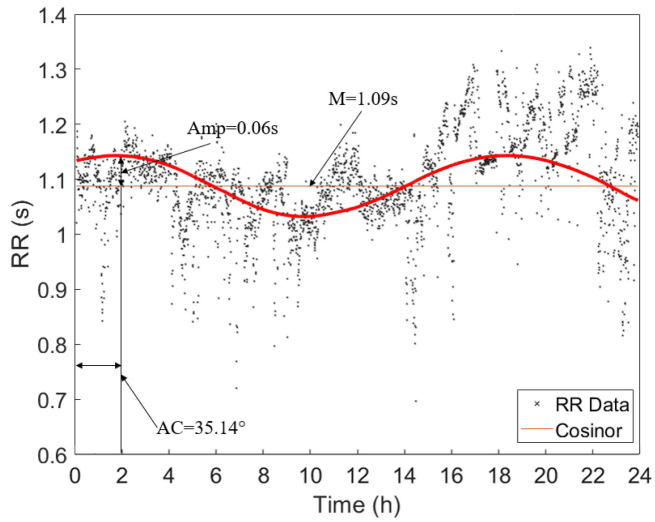


Fig. 2. An example of 24-h Cosinor analysis applied on a selected heart rate variability data.

C. HRV Features

The selected HRV features included time-domain and frequency-domain based features [36]. Several HRV features were selected from non-linear metrics, including Poincare plot, detrended fluctuation analysis (DFA) [37], and multiscale entropy (MSE) [38], as well as features from HRV fragmentation indices [39]. The features were extracted using MATLAB R2020a software using the PhysioNet toolbox and function (`mhrv()`) [40]. A brief description of these features is shown in Table II.

TABLE II
HEART RATE VARIABILITY (HRV) FEATURES DEFINITIONS [40]

Number	Feature	Definition
1	**AVNN (ms)**	Average N-to-N interval
2	**SDNN (ms)**	Standard deviation of the N-to-N intervals
3	**RMSSD (ms)**	Square root of the mean of the sum of squares of differences between adjacent N-to-N intervals
4	**pNN50 (%)**	Percentage of N-to-N intervals $>$ 50ms
5	**SEM (ms)**	Standard error of the average N-to-N interval
6	**BETA**	Slope of the linear interpolation of the spectrum for frequencies less than VLF band upper bound
7	**HF Norm (%)**	Normalized HF power
8	**HF Peak (Hz)**	Peak frequency in the HF band
9	**HF Power (ms^2)**	Power in the HF band
10	**LF Norm (%)**	Normalized LF power
11	**LF Peak (Hz)**	Peak frequency in the LF band
12	**LF Power (ms^2)**	Power in the LF band
13	**LF/HF**	LF power to the HF power ratio
14	**Total Power (ms^2)**	Total power in both frequencies bands
15	**VLF Norm (%)**	Normalized VLF power
16	**VLF Power (ms^2)**	Power in the VLF band
17	**SD1 (ms)**	Standard deviation of the N-to-N intervals along the perpendicular to the line-of-identity
18	**SD2 (ms)**	Standard deviation of the N-to-N intervals along the line-of-identity
19	**Alpha1**	Detrended fluctuation analysis low-scale slope
20	**Alpha2**	Detrended fluctuation analysis high-scale slope
21	**Sample Entropy**	Complexity of physiological time-series signals
22	**PIP (%)**	Percentage of inflection points in the N-to-N interval
23	**IALS**	Acceleration/deceleration segments inverse average length
24	**PSS (%)**	Percentage of short segments
25	**PAS (%)**	Percentage of alternation segments

D. Support Vector Regression (SVR)

In this study, a Support Vector Regression (SVR) model was selected for the training and testing process as these are more generalized and provide an output with continuous values [41]. Suport Vector Machine (SVM) algorithms are commonly used for their ability of finding an optimum hyper-plane that separates the data with a maximum margin.SVMs differ from other Neural Network classifiers in using regularized empirical risk minimization (ERM) instead of traditional ERM, which prevents over-fitting and poor generalization when using small data sets [19], [42].

In SVR, an ϵ-insensitive tube is introduced to approximate a function with a balanced prediction error and model complexity [43]. The input data are mapped into a high dimensional feature space, where the classification/regression problem is treated as a linear problem [19]. More information on the mathematical formulation of SVR models is provided in [44].

E. Training and Testing

The training and testing process for the SVR analysis went through two phases. The first was to use the full feature set of the 25 features (Table II) to estimate the values of LVEF at each hour of the 24 hour circadian cycle. The second was to decide which feature set provided the best LVEF predictions and apply this for the final LVEF estimations and evaluations.

1) 25 Features Set: Initially, the full feature set of 25 HRV features described in Table II was used to train the SVR and to estimate hourly HRV levels. A leave-one-out (LOO) training and testing scheme was then followed. LOO was preferred over other training schemes, such as k-folds, to include the maximum possible data within the training set. In addition, a k-fold training scheme would cause some leakage of data when predicting patient by patient LVEF value. The training process was repeated at each iteration across all patient sets until an optimal prediction for the LVEF was obtained for each patient. To evaluate the regression model at each hour over the 24 hour recording, the Root Mean Square Error (RMSE) was calculated between the original and predicted LVEF values. The hourly models were trained using linear, RBF, and polynomial kernel functions. The selection of the parameters for the three functions included several trial-and-error tests under different values for ϵ and C. The optimal choice of these two parameters ensures no over-fitting in the model.

2) Feature Selection: The SVR training and testing process followed a step-wise feature selection approach to determine the best HRV features from the 25 available for estimating LVEF based on optimmizing the RMSE values for each hourly interval [45], [46]. In this approach, the feature selection process was allowed to run for 25 iterations to cover all the 25 HRV features. For each hourly interval, and for the first iteration, features were added one by one and used to train the model,

TABLE III
THE SELECTION OF THE BEST FUNCTIONS' PARAMETERS AT HOUR 18:00-19:00. THE BEST PARAMETERS ARE HIGHLIGHTED IN BOLD

Kernel Function	ϵ	C	RMSE
Linear	**0.5**	0.1	12.3
		0.25	12.0
		0.5	**11.5**
RBF	**0.25**	0.25	13.1
		0.5	12.9
		16	**12.7**
Polynomial (d=1)	**0.1**	0.25	11.9
		0.5	11.8
		1	**10.7**

make LVEF estimations, and obtain the corresponding RMSE values. The feature that provided the lowest RMSE value was added to the best feature set. Then, on the second iteration, the remaining 24 features were added one by one to the best feature set (which includes the feature picked from the previous iteration) and used to train the model, make LVEF estimations, and obtain the RMSE value. This was performed to achieve the best combination of features based on the lowest RMSE values on every iteration. This process was iteratively repeated to ensure all 25 HRV feature combinations were included. If, for example, the remaining 23 features after the second iteration do not decrease the RMSE value, the process is stopped and the best feature set includes only two features from iterations 1 and 2.

The best feature combination having the lowest RMSE was considered the optimal set of classifier features for each hourly interval. Finally, the best per-hour feature sets were used once again to train the model, and obtain the final predictions of the LVEF values for each patient. The final estimations of the hourly LVEF were evaluated using Bland-Altman and correlation analysis.

III. RESULTS

Table III shows the best parameters selected for each kernel function at a selected sample hour (6 pm - 7 pm) using the whole 25 HRV features. The lowest RMSE values were obtained when using the polynomial kernel of order 1 with ϵ set at 0.1 and C at 1. Using the function parameters shown in bold, Table IV shows the hourly RMSE values between the original and estimated LVEF values following the first training and testing scheme using the full 25 features set. The lowest RMSE value (10.7) was obtained between 6 pm and 7 pm using the polynomial kernel function.

The best features set selection approach is illustrated in Fig. 3 for the 5am to 6am hourly interval using the RBF kernel function. At this time interval, the RMSE values decreased as features were added to the set until iteration number 9 (RMSE = 10.5), which means nine features were added to the best feature set at this hour. Furthermore, Fig. 4 ranks all features as per their number of occurrences for each hourly interval throughout the

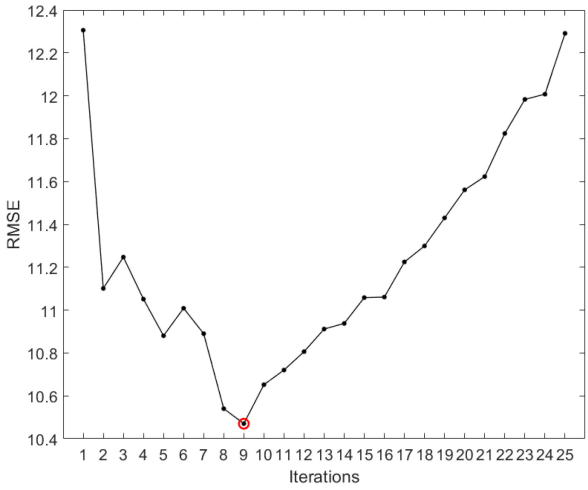


Fig. 3. RMSE per features set at hour 05:00-06:00 with RBF kernel function. The Red circle shows the iteration to stop adding features.

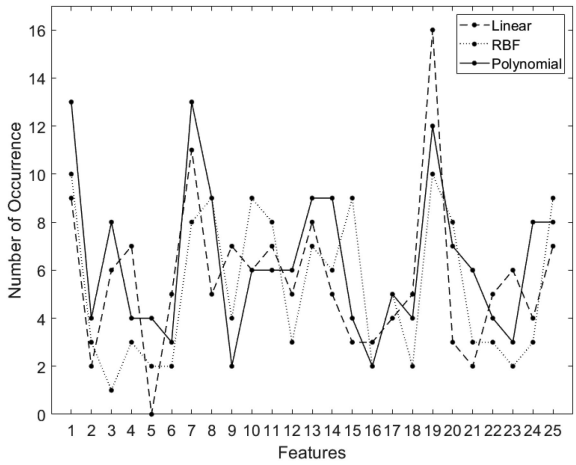


Fig. 4. Ranking each feature as per the number of occurrence throughout the hours using the three kernel functions.

24 hours using the three kernel functions. From the plot, the highly favored features to be included within the best feature sets were AVNN, HF Norm, and alpha1. In addition, the pattern shows that the frequency-domain features appeared more than other features

The results of the new hourly RMSE values are shown in Table V using the best feature set. From the latter, the lowest RMSE values occurred between 3 am to 4 am and 5 am to 6 am, using the RBF kernel function, and at 6 pm to 7 pm, using the polynomial kernel function. The best feature sets at these hours included:

- **Hour 03:00-04:00:**
  HF Norm, LF/HF, VLF Norm, Alpha1, Alpha2, PAS
- **Hour 05:00-06:00:**
  AVNN, SDNN, HF Power, LF Peak, LF/HF, VLF Norm, SD1, Alpha1, PSS
- **Hour 18:00-19:00:**
  AVNN, SDNN, RMSSD, SEM, BETA, HF Norm, HF Peak, LF Norm, LF Peak, LF Power, LF/HF, Total Power, SD1, SD2, Alpha2, Sample Entropy, PSS, PAS

TABLE IV
HOURLY RMSE BETWEEN ORIGINAL AND ESTIMATED LVEF VALUES USING 25 FEATURES SET

Kernel	ϵ	C	00-01	01-02	02-03	03-04	04-05	05-06	06-07	07-08	08-09	09-10	10-11	11-12	12-13	13-14	14-15	15-16	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24
Linear	*0.5*	*0.5*	12.5	14.3	12.4	12.9	15.0	13.8	13.4	12.4	13.3	14.4	12.2	13.6	13.3	12.7	12.6	13.1	12.8	12.7	11.5	14.6	12.8	14.4	12.5	14.1
RBF	*0.25*	*16*	12.5	12.9	12.4	12.4	12.9	12.3	12.8	12.9	13.0	13.0	13.3	14.3	14.3	13.6	13.0	12.7	13.8	14.1	12.7	13.6	13.2	13.6	12.7	13.8
Polynomial (d=1)	*0.1*	*1*	12.9	16.1	13.1	13.2	15.5	14.7	13.9	12.7	13.0	15.1	11.9	14.1	14.3	12.9	12.8	13.3	12.0	13.2	**10.7***	16.4	12.9	15.4	12.5	15.7

** The star represents the lowest RMSE value.*

TABLE V
HOURLY RMSE BETWEEN ESTIMATED AND ORIGINAL LVEF VALUES USING BEST FEATURES SET

Kernel	ϵ	C	00-01	01-02	02-03	03-04	04-05	05-06	06-07	07-08	08-09	09-10	10-11	11-12	12-13	13-14	14-15	15-16	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24
Linear	*0.5*	*0.5*	11.1	11.3	11.4	11.5	12.1	11.4	11.9	11.8	12.0	12.2	11.3	12.0	12.2	12.0	11.7	11.7	11.3	11.7	10.9	12.2	12.1	11.9	11.5	11.4
RBF	*0.25*	*16*	11.2	11.8	11.6	**10.6***	11.2	**10.5***	10.9	11.5	11.0	11.1	11.0	11.3	11.9	11.8	11.5	11.6	11.3	11.7	11.3	11.8	11.9	11.8	11.2	11.5
Polynomial (d=1)	*0.1*	*1*	11.0	11.3	11.3	11.6	12.0	11.4	11.7	11.6	11.8	12.4	11.2	11.7	12.2	11.8	11.8	11.4	11.1	11.8	**10.4***	12.2	11.9	11.9	11.3	11.5

** The stars represent the lowest RMSE values.*

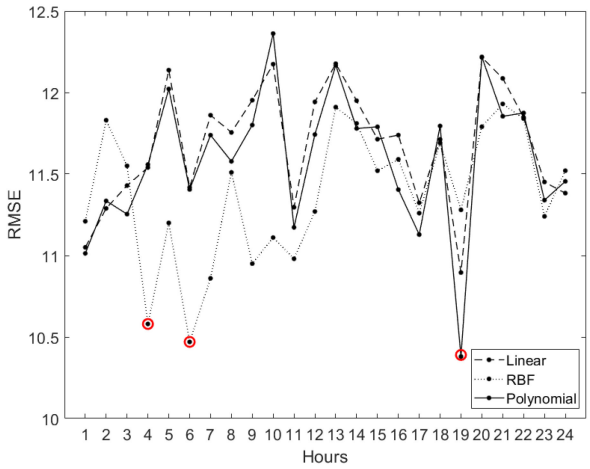


Fig. 5. RMSE per hour using the best features set for the three kernel function. Red circles show the hours of occurrence of the lowest RMSE values.

TABLE VI
ORIGINAL AND ESTIMATED LVEF VALUES FOR THE CORRECTLY IDENTIFIED MID-RANGE EF CASES FOLLOWING BOTH CLASSIFICATION SCHEMES AT THE THREE BEST HOURS

	Best Hours		
	03:00-04:00	**05:00-06:00**	**18:00-19:00**
Mid-range EF Classification 1 Original% (Estimated%)	55 (55.07)	55 (53.74)	50 (52.85)
	54 (50.19)	55 (51.39)	53 (52.81)
	52 (51.97)	55 (52.92)	50 (50.61)
	55 (52.39)	-	55 (53.24)
Mid-range EF Classification 2 Original% (Estimated%)	46 (46.20)	46 (45.28)	46 (49.69)
	49 (45.29)	45 (41.78)	49 (47.41)
	46 (46.12)	48 (49.34)	44 (45.35)
	45 (45.38)	45 (48.41)	46 (46.55)
	41 (48.09)		45 (45.64)
	49 (49.59)	-	45 (48.97)
	48 (46.97)		50 (47.41)
	50 (48.33)		-

The lowest error (RMSE = 10.4) occurred between 6pm to 7pm using the polynomial kernel function, where 18 features out of the 25 were included, whilst the linear kernel function led to an RMSE value of 10.9 at this time interval. In addition, Fig. 5 depicts the RMSE distribution across the 24 hours using the three kernel functions. In the latter, the time interval of the lowest possible RMSE values discussed are highlighted in red.

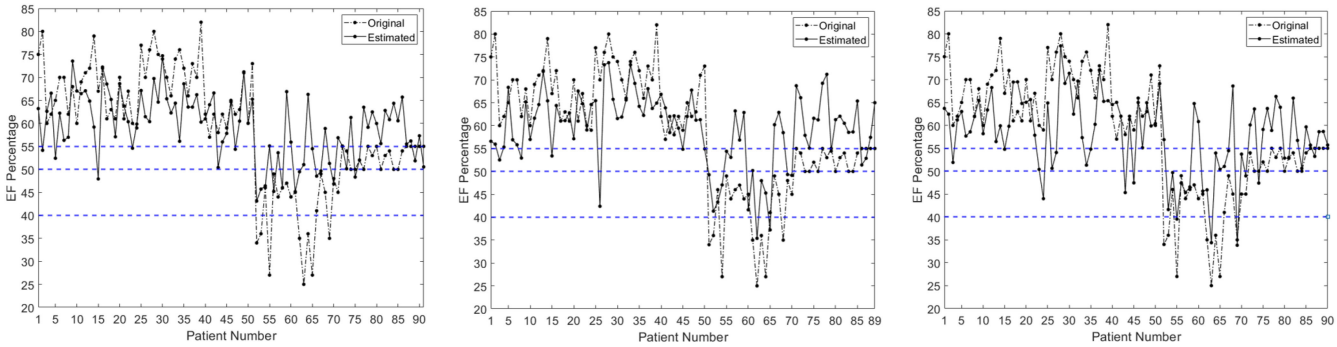
Furthermore, Fig. 6 shows the original and estimated LVEF values for all patients at 03:00-04:00 h, 05:00-06:00 h, and 18:00-19:00 h with the lowest RMSE values. The blue lines represent the range of the two mid-range LVEF classifications described in Section II.

Based on LVEF classification 1, the 20 mid-range patients ($50\% \leq \text{EF} \leq 55\%$) were mostly over-estimated across the three-hourly intervals; which means that the SVR model predicted most patients to be within the normal group (EF $> 55\%$). Only four patients between 03:00-04:00 h and 18:00-19:00 h and three patients at the 05:00-06:00 h interval were estimated correctly as mid-range cases. Two patients were estimated as at-risk (EF $< 50\%$) cases at 03:00-04:00 h and 18:00-19:00 h.

Based on ACCF/AHA LVEF classification, the number of correctly identified mid-range patients ($40\% \leq \text{EF} \leq 50\%$) was higher than that for the ASE/EACVI classification. Out of the 19 patients within the $40\% \leq \text{EF} \leq 50\%$ range, eight, four, and seven patients were estimated correctly as mid-range cases, albeit at different hourly intervals (3-4 am, 5-6 am, and 6-7 pm, respectively). The remainder were estimated as normal cases (EF $> 50\%$), with only one case having an estimated LVEF value in the at-risk range (EF $< 40\%$) at 05:00-06:00 h.

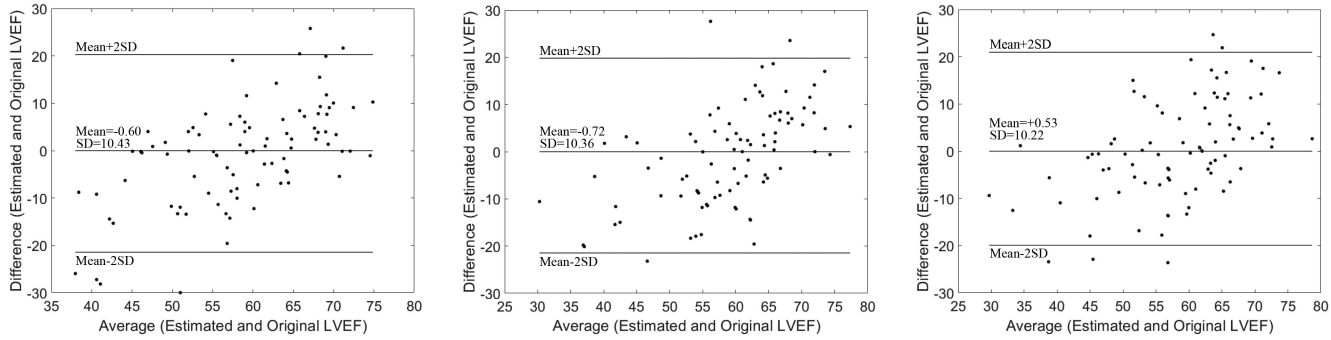
Table VI shows the original and estimated LVEF values for the correctly identified mid-range EF cases when following both classification schemes for the 3-4 am, 5-6 am, and 6-7 pm intervals.

To elaborate more on the prediction model, Figs. 7 and 8 show the Bland-Altman and correlation plots, respectively. The mean bias was underestimated at 3-4 am and 5-6 am, and overestimated between 6 pm and 7 pm. Furthermore, the highest correlation coefficient occurred at 6-7 pm with 0.61 and a p-value of 3×10^{-10}, whereas the correlation at 3-4 am and 5-6 am was 0.57 and 0.60, respectively.



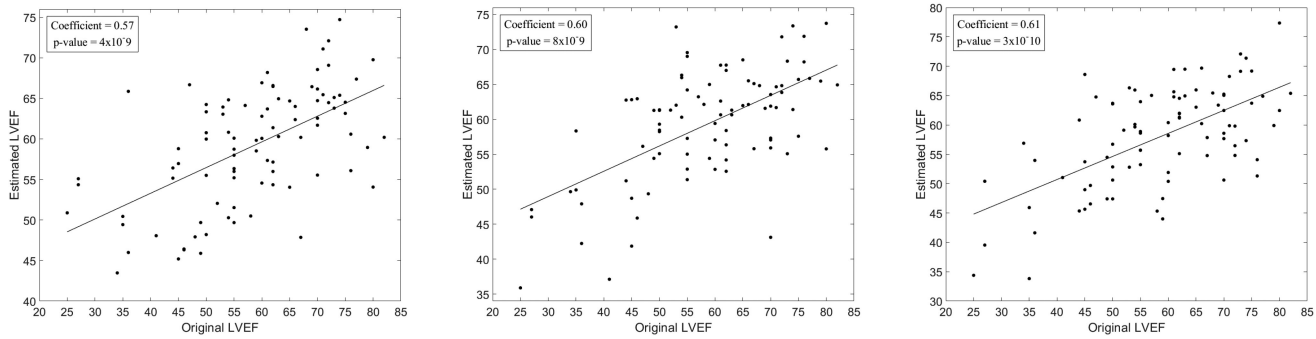
(a) 03:00-04:00 (b) 05:00-06:00 (c) 18:00-19:00

Fig. 6. Original and estimated LVEF values per patient for hours (03:00-04:00, 05:00-06:00) using RBF kernel and (18:00-19:00) using polynomial kernel. The blue lines show the mid-range limits following both LVEF classifications.



(a) 03:00-04:00 (b) 05:00-06:00 (c) 18:00-19:00

Fig. 7. Bland-Altman plots between the average value of (Original and estimated LVEF) and their corresponding difference for hours (03:00-04:00, 05:00-06:00) using RBF kernel and (18:00-19:00) using polynomial kernel.



(a) 03:00-04:00 (b) 05:00-06:00 (c) 18:00-19:00

Fig. 8. Correlation plots between the original and estimated LVEF values for hours (03:00-04:00, 05:00-06:00) using RBF kernel and (18:00-19:00) using polynomial kernel.

IV. Discussion

A. SVR Model

The low values obtained for ϵ shown in Table III support the definitions found in the literature [43]. On the other hand, the higher values selected for C reflect the need to minimize only the empirical risk regardless of the model complexity

Across the three kernel functions, the polynomial function of order $d = 1$ provided the lowest RMSE value at 6-7 pm, which improved slightly following the feature selection approach for the same hourly interval. This can be explained by the fact that SVR uses polynomial kernels to represent similarities between the training samples in the higher dimensional feature space. Thus, for regression problems and unlike other kernel functions, SVR is better at finding the non-linear interactions between the features when creating the learned hyperplane [44].

After enhancing the performance of the SVR for the 24 hourly intervals, the RBF kernel function provided similar results to the polynomial function at 3-4 am and 5-6 am. In addition, Fig. 5 shows that the RBF function provided lower errors than

other functions during the early morning hours 4-9 am. It is worth noting that the linear function did not provide interesting observations except between 6-7 pm.

B. 24-Hour Analysis of Features

This study provides insight into the behavior of the HRV features on an hourly basis. Certainly, not all HRV features are meaningful if the length of the recording is decreased to less than an hour if the purpose is to investigate the 24-h circadian rhythm of the heart. The DFA, which requires a 2-hour recording [47], optimally, in as an example in this category. Using the 25 features simultaneously for the training of the SVR model did not provide the desired performance in estimating LVEF values, which may be due to changes in cardiac performance over the 24-hour recording time for each patient. The observations show that at every hourly interval, several features were very similar across the three patient groups, that is, the SVR model could not distinguish between the corresponding patient LVEF levels or range. To elaborate more on the importance of features, a per-hour step-wise feature selection approach ensures that all possible feature combinations for the 25 HRV features were included. This approach provides many advantages, including its ability to fine-tune the model at every hourly interval and obtain the lowest possible errors. Additionally, not all HRV features have the same discriminatory ability between CAD patients, especially with regard to their LVEF levels at every hour. For example, the lowest observed RMSE occurred at 6-7pm, but required 18 iterations. Apart from the step-wise approach, other feature extraction methods have been tested, such as Minimum Redundancy Maximum Relevance (mRMR) [48] yet, experimental results have shown that the step-wise approach has resulted in lower RMSE values. For example, at 3-4pm, the same features were observed, however, an extra feature was added to the best feature set (alpha2) using the step-wise method that resulted in a lower RMSE value (mRMR $=$ 10.8, step-wise $=$ 10.6).

Across the 24 hours, the best features were AVNN, HF Norm, and Alpha1. The alpha1 HRV feature was found to be the best feature for classification across all hourly intervals, being included 18 times using the linear function and included in the three-hourly intervals with the lowest RMSE. In addition, the importance of HF Norm and Alpha1, both being high frequency metrics reflect the feasibility of using HRV in understanding the effect and development of heart failure in CAD patients as these are markers for parasympathetic nervous system function.

C. Clinical Relevance

The circadian 24-h cycle analysis is essential when evaluating CAD patients based on their LVEF levels. Unlike other cardiac arrhythmias, the cardiac dysfunction, be it mechanical or rhythm related, may not be evident at all times during the 24 hour ECG recording. Our results indicate that circadian rhythm analysis led to identifying hourly intervals where the estimated LVEF not only correlated best with the clinically derived LVEF values but also corresponded to previously reported high-risk times between 7 am to 11 am and 6 pm to midnight for myocardial infarcts and increased mortality [49]–[52].

At this stage the use of echocardiography is not routinely undertaken for HF patients, and patients with mid-range LVEF may in fact have preserved heart function. However, HRV analysis for determining LVEF can be undertaken more often, and hence disease progression can be identified in a more timely manner.

HRV is a response to changes in autonomic nervous system modulation, intrinsic cardiac regulation (e.g., SA node) and mechanical factors. These are dynamic and change as requirements changes throughout the day. Hence, HRV features that provide information on the global attributes of the time series, such as SDNN may not be sensitive to heart rate characteristics associated with more subtle modulatory changes such as RMSSD or entropy measures. An example is the sympathetic surge occurring in the early morning and late afternoon that may be better identified with Poincaré Plot analysis [33].

The current findings pave the way for applying cardiovascular chronopharmacology more effectively as the results provide specific hourly intervals where LVEF corresponds best with HRV in mid-range LVEF patients. The effects of chronopharamacology on cardiac rhythm have not been extensively investigated however, several studies have indicated a time-of-day influence of cardiac medication on cardiac rhythm [26].

For mid-range LVEF, the estimated LVEF values derived from 24-hour HRV features corresponded more closely to the ACCF/AHA LVEF classification, suggesting that lower LVEF findings using echocardiography may have a stronger autonomic nervous system component. For the ASE/EACVI classification, HRV estimated LVEF was more prone to indicate a preserved ejection fraction function. Following the ACCF/AHA, better estimations were observed, as reflected by more patients correctly estimated within the mid-range group. This suggests that LVEF at this mid-range LVEF border-line is better correlated with changes in HRV.

V. Conclusion

This study suggests that HRV features derived from 24 hour ECG recordings provide a promising alternative to the current echocardiography gold standard for determining LVEF levels in CAD patients. Future work will include the use of deep-machine learning algorithms to improve LVEF classification further using HRV features. In addition, the use of clinical data to validate the proposed procedures will also be considered.

Acknowledgment

The authors would like to thank Khwaja Y. Hasan from the Cardiology Department at Cleveland Clinic, Abu Dhabi for his advices on classification of LVEF in heart failure patients and the Telemetric and Holter ECG Warehouse (THEW) for providing the data.

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