Discrimination Between Normal-to-Mild and Severe Coronary Artery Disease using Time-Domain Features of the Finger Photoplethysmogram Response to Reactive Hyperemia

Abstract:

Atherosclerosis is one of the major causes of coronary artery blockage leading to morbidity and mortality worldwide. Currently, coronary angiography is considered to be the most accurate technique to diagnose coronary artery disease (CAD). However, coronary angiography is an invasive and expensive procedure posing risks of serious complications such as heart attack. Since the symptoms of CAD are not noticed until the advanced state of the disease, early and effective diagnosis of CAD is considered as a pertinent measure.

In this paper the finger photoplethysmogram (PPG), a non-invasive optical signal, obtained before and after reactive hyperemia is proposed to discriminate between subjects with normal-to-mild and severe CAD. To this end, the PPG from left and right index fingers and standard 3-lead ECG of 37 patients scheduled for angiography were recorded. Of these 37 patients, 21 were diagnosed by three expert cardiologists as having no or mild blockage only, whereas the remaining 16 had severe blockage. The flow-mediated dilation test was performed on each subject under standard conditions, and various time-domain features were tested using a k-nearest neighbor classifier. The best performance was obtained for a combination of the following features: crest time, rising velocity and pulse transit time, giving an accuracy of 87.5%, a sensitivity of 77.0% and specificity of 97.9%. We submit that this technique can be proposed to implement an efficient triage system useful for scheduling coronary angiography, as it is able to identify non-invasively patients at greater risk of coronary blockage.

Keywords: Photoplethysmogram, ECG, coronary blockage, triage.
I. BACKGROUND

A- CAD and Endothelial Dysfunction

Accumulation of atheromatous plaques made up of fatty matters (e.g. cholesterol) within the walls of the coronary arteries is the major cause of coronary artery disease (CAD) [1]. Atherosclerosis, the subsequent thickening and hardening of the coronary artery walls, is considered as the main cause of coronary artery blockage [2]. The deposition of plaque in the arteries limits the blood flow to the cardiac muscle leading to myocardial infarctions and heart attacks. CAD has been identified as one of the leading causes of morbidity and mortality worldwide whereas ischemic heart disease has been the first cause of death throughout the world in 2008 [3]. In the European Union alone, CAD's financial burden is estimated €45 billion in 2003 [4].

Several tests do exist for CAD diagnosis: coronary angiography, intravascular ultrasound and exercise electrocardiography (ECG) [1]. Although considered as the gold standard in detecting CAD, coronary angiography is an invasive method with serious complications risks from one to two per thousand [5]. Intravascular ultrasound (IVUS) is reported to have an accuracy of 61%, sensitivity of 53% and specificity of 69% in discriminating between subjects with and without coronary blockage [6]. Depending on the protocol, exercise ECG has a sensitivity of 25% to 71% for patients with one artery occlusion [1]. In patients with two or three artery occlusions, exercise ECG is reported to have a sensitivity of 81% and a specificity of 66% [1]. The serious outcomes of CAD emphasize the difficulty in finding the right balance between accuracy, convenience for the patient and economical aspects of the proposed screening tests.

Since the symptoms of the disease are noticed only at an advanced state, CAD screening is a crucial averting measure. It is known that the function and the structure of vessels are impaired well before any observation of cardiovascular disease (CVD) symptoms is possible [7]. More specifically, endothelial dysfunction (ED) is considered as one of the primary reasons of artery sclerosis and ischemic heart disease [8], and it has been found to be closely associated with cardiovascular events (p<0.05) [9][10]. Thus, the study of ED may be considered as one of the methods to indirectly establish a prognosis of atherosclerosis and CAD [8].

B- Endothelial Dysfunction Assessment Techniques

The main anatomical site of interest in evaluating the ED is the aortic arch, as its diameter conditions the amount of hemodynamic resistance the left ventricle is faced with during systole. The next sites of interest are the coronary arteries as they supply blood to the myocardium. A key quantifiable feature of ED is the inability of the aortic wall to fully dilate in response to a physical or chemical stimulus to release vasodilators (i.e. nitric oxide) [11]. Access to the coronary arteries and aortic arch being only possible through invasive means, a surrogate site has been proposed: the brachial artery [12]. It has been shown that the endothelial function in
brachial and coronary arteries are correlated ($r=0.41$, $p=0.003$) [12]. Thus, a plausible measure in assessing the endothelial function in coronary arteries and subsequently the presence of CAD would be to examine the endothelial function in brachial arteries.

The most widely used non-invasive test for evaluating the endothelial dysfunction in brachial arteries is the flow-mediated dilation (FMD) test [11]. During FMD, reactive hyperemia is induced via temporary artery occlusion and the resultant relative increase in brachial artery diameter is measured by B-mode ultrasound (US-FMD). This technique is considered costly since it requires high-frequency (> 10 MHz) probes in order to get high-resolution (< 100 μm) images. Furthermore, the accuracy of the results depends highly on the skills of the operator.

An alternative method to US-FMD has been proposed in assessing the endothelial function in the FMD test using the photoplethysmogram signal (PPG) [13]-[16]. The PPG, as comprehensively studied in [13], represents the volumetric changes in blood vessels and can easily be recorded by a sensor consisting of a light source and a photo detector. The principle of PPG is that the light (mainly red, infrared or green light) traveling through biological tissues (e.g. the fingertip or earlobe) will be absorbed by different tissues (skin, muscle, fat, bone, arterial and venous blood). The arteries contain more blood during systole than diastole, as their diameter changes due to the blood pressure pulses. The detected light reflected from (reflective mode PPG) or transmitted through (transmissive mode PPG) the vessels will thus fluctuate synchronously with the pulsatile blood circulation. The advantages of PPG include easy set up, simple operation and low cost. It is also possible to record the PPG without any direct contact with the skin surface [13]. The above advantages may explain why PPG technology has attracted much attention in clinical applications [13]. Among these, there have been attempts to assess the endothelial function and presence of CAD through PPG signal processing in the FMD test [14]-[16].

C- Scope of This Work

Our objective is to propose a classification method using PPG to effectively discriminate between different coronary artery blockage conditions. To this end, a thorough set of time-domain features are extracted from the PPG. As we use the standard occlusion test and investigate the FMD via PPG, we shall refer to our technique as PPG-FMD. Using a vast set of time domain features, we submit that it is possible to improve the classification results of previous attempts [14]-[16] in which only one or two time-domain features were considered.

The rest of the article is organized as follows. Section II describes the details of the performed FMD test including our in-house developed setup, the subject's characteristics ad preprocessing measures. Then the extracted features of the PPG and the implemented classification and feature selection algorithms are described. Section III will elaborate on the
selected features and the classification results. Finally, section IV concludes our work by presenting a general view of possible future works.

II. EXPERIMENTAL ASPECTS

A. Subjects Description

A total number of 48 subjects (16 female and 32 male) were recruited for this study. The subjects were patients scheduled for coronary angiography at the Tehran Heart Center (THC). The study received ethical clearance from THC and informed written consent was obtained from all subjects according to the Declaration of Helsinki [19]. The data acquisition was performed the day before subjects were due for their angiography. One the angiography done, the subjects were labeled by three expert cardiologists from THC using the following scale: NC (Normal Condition), Mild, SVD (Single Vessel Disease), 2VD (Double Vessel Disease) and 3VD (Triple Vessel Disease). All diagnoses were unanimous except for two cases where a majority vote of the cardiologists opinions was taken as the true labels. Angiography labels and the age of the subjects are summarized in Table 1.

<table>
<thead>
<tr>
<th>Label from Expert Cardiologist</th>
<th>N (Female/Male)</th>
<th>Age (Mean±S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Condition (NC)</td>
<td>18 (11/7)</td>
<td>55.4 ± 10.9</td>
</tr>
<tr>
<td>Mild</td>
<td>3 (1/2)</td>
<td>55 ± 4.1</td>
</tr>
<tr>
<td>Single-Vessel Disease (SVD)</td>
<td>11 (3/8)</td>
<td>60.7 ± 10.2</td>
</tr>
<tr>
<td>2-Vessel Disease (2VD)</td>
<td>5 (0/5)</td>
<td>65.2 ± 6.6</td>
</tr>
<tr>
<td>3-Vessel Disease (3VD)</td>
<td>11 (1/10)</td>
<td>60.9 ± 10</td>
</tr>
<tr>
<td>Total</td>
<td>48 (16/32)</td>
<td>58.9 ± 9.6</td>
</tr>
</tbody>
</table>

B. Final Groups

As the number of subjects may be low for particular categories (Table 1), new groups of subjects were formed. To this end, the initial NC and mild subject were put in Group 1, the SVD subjects in Group 2 and finally the 2VD and 3VD subjects in Group 3. This approach allowed us to have a more remarkable number of samples in each group whereas keeping the affinity of the subjects regrouped on each newly defined Group. Table 3 shows the characteristics of each of these three groups with full details of their health status (history of diabetes, hypertension, hyperlipidemia, statistical measures of height, weight and lipid profile).
C. PPG-FMD Protocol

The flow-mediated dilation (FMD) test was conducted using the standard procedure proposed in [17]. The only difference being that ultrasound imaging was not employed, as our aim was to assess PPG-FMD. Before starting the test, a brief explanation was given to subjects in order to familiarize them with the equipment and reduce their anxiety. Subjects were asked to fast overnight. All subjects were in the supine position throughout the test and the PPG probes were attached to the left and right index fingers whereas the rapid inflator's cuff was attached to the test arm above the elbow. The ECG was also recorded using a 3-lead system. The right arm on which the FMD test was implemented is called the test arm, and the left arm which was in the state of rest throughout the experiment is called the control arm. Prior to performing the test, the systolic and diastolic pressures were measured using an automatic sphygmomanometer with the cuff positioned over the control arm. The duration of the FMD test was twelve minutes split into three phases. All signals were continuously recorded during these 3 phases.

Phase 1: consists of the first two minutes, where control and test arms were in the state of rest.
Phase 2: starts at the third minute, where the pressure of the cuff attached to the test arm was increased to 35 mmHg above the subject's systolic pressure. The cuff pressure was maintained for the five minutes.

Phase 3: the cuff was rapidly deflated which brought about the instantaneous blood flow through the test arm.

Fig. 1. Example of recorded PPG during FMD test: (a) Test arm (b) Control arm

D. Data Acquisition Setup
An in-house 2-channel PPG recording system was built in the Biomedical Engineering Laboratory at Sharif University of Technology which used the standard red wavelength (660 nm). This system incorporated a low-pass filter with a cut-off frequency of 20 Hz [15]. The two PPG probes were attached to the right and left index fingers of the test subjects. A 5-lead chest ECG amplifier board was also developed in-house. All analog signals were fed into a Power Lab/16 SP (AD Instruments Inc.) for the purpose of A/D conversion at a resolution of 16 bits. This allowed all data to be recorded simultaneously at a sampling rate of 2 kHz. The digitalized outputs were displayed in real-time on a computer monitor using the available commercial software Chart5 (AD Instruments Inc.). Besides the native Chart5 format, all signals were saved under ASCII text format for further offline processing.

The standard FMD protocol [ref guidelines FMD Harris] states the requirement for cuff inflation. Such an inflator has to be able to increase the cuff pressure up to 50 mmHg above the systolic pressure and release it in less than 300 ms. Such a system was developed in the Biomedical Engineering Laboratory at Sharif University of Technology. The recorded PPG signals of a single test subject are shown in Fig. 1. Throughout the tests, the left and right arms were the control and test, respectively.

III. PREPROCESSING

In order to prepare the signals for feature extraction and minimize the errors, three types of preprocessing were implemented: downsampling, detrending and left-right AC normalization. These steps are described in the following lines.

A. **Downsampling:** The original sampling rate of the signals was 2 kHz which was reduced to 100 Hz by downsampling. This allowed the size of data and decrease the computational time.

B. **Detrending:** Since the baseline of the PPG signal is affected mainly by respiration which is not relevant to the endothelial function, the DC component or the baseline of the PPG signal was eliminated using the Wavelet transform [20]. From now on, the detrended AC part of the PPG will be referred to as "PPG".

C. **Amplitude normalization**

It is well known that the amplitude of the PPG is affected due to different tissue optical properties (mainly due to variations in color and thickness). Besides this factor, natural spontaneous variations in the PPG occurs due to autonomic changes [15][16].
The objective of the normalization measure is to separate the autonomic changes from those induced by the FMD test. The key observation here is that the test arm PPG is affected both by the effects of FMD and autonomic changes, but the control arm is only affected by autonomic changes. It is also known that there exist a linear relationship between the PPG of left and right index fingers [ref]. Therefore, the following normalization procedure to eliminate the effects of autonomic changes is proposed:

Conventions:

- PPG\text{test} = \text{PPG of the finger of the arm undergoing FMD},
- PPG\text{ctrl} = \text{PPG of the finger of the control arm}.

- In phase 1: using measured PPG\text{test} and PPG\text{ctrl} at rest, compute the coefficients of the linear regression:

\[
PPG_{\text{test arm}} = PPG_{\text{control arm}} \times m + c \tag{1}
\]

where m and c are two constants that are determined empirically. An effective method to obtain this estimation is proposed in [16]: first a linear regression (1) of the test arm’s PPG signal on the control arm’s PPG signal is performed while both arms are in a state of rest (i.e. phase 1). An exemplification of such a regression is displayed in Fig. 2. Note that parameter c is negligible because of the DC removal from all PPG prior to feature extraction.

- In phase 3 (release):
  - estimate $\overline{PPG}\text{test}$, the part of PPG\text{test} amplitude changes which is due to autonomic changes. This estimation represents what the PPG amplitude would have been if no FMD stimulus had been given.
  - To eliminate the non-FMD related effects, divide PPG\text{test} by $\overline{PPG}\text{test}$. Note that under rest conditions, the test arm PPG would have an amplitude of one once this normalization is implemented.

\[
PPG_{\text{norm}} = \frac{PPG_{\text{test}}}{m \times PPG_{\text{ctrl}} + c} \tag{2}
\]
The above normalization measure eliminates any effect present in the PPG signal of both arms. Thus the autonomic changes in the PPG signal are separated from those induced by the FMD test. For the sake of simplicity, we will refer to the normalized signals and features without the "norm" subscript. Therefore, PPG is the normalized PPG.

C- Considered interval

The duration of phase 3 of the FMD test is 5 minutes but not all this time is usable. Artifacts due to the cuff release are present during the first few seconds and the PPG reaches its steady state after approximately 3 to 4 minutes. Another observation was that the last few seconds of data were also affected by motion artifacts, probably due to the operator informing the subject about the imminent end of the data acquisition. Therefore all signals were considered for processing between the first 10 seconds and the last 20 seconds of phase 3 (4.5 minutes in total).

III. Classification

Phase 3 of our PPG-FMD test (Fig. 1) contains the response of the endothelium to the stimulus which was provided by releasing the cuff. Thus, in order to effectively implement the classification process, relevant time-domain features of the recorded PPG signal in phase 3 of the FMD test were extracted.

A- Feature Extraction

As proposed in [21] and [22], key characteristics of a single PPG pulse in the time domain are summarized in Table 2 and depicted in Fig. 3.

<p>| TABLE 2: TIME DOMAIN FEATURES DEFINED OVER ONE PPG CYCLE |</p>
<table>
<thead>
<tr>
<th>Feature</th>
<th>Name</th>
<th>Abbreviation</th>
<th>Description (S = systolic peak; D = diastolic valley)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amplitude</td>
<td>AC</td>
<td>The amplitude difference between S and D</td>
</tr>
<tr>
<td>2</td>
<td>Crest Time</td>
<td>CT</td>
<td>The time it takes for the pulse to reach S from D</td>
</tr>
<tr>
<td>3</td>
<td>Stroke Volume</td>
<td>SV</td>
<td>The area under the signal and the line joining two consecutive D</td>
</tr>
<tr>
<td>4</td>
<td>Rising Velocity</td>
<td>RV</td>
<td>The initial positive slope: ( \frac{AC}{CT} )</td>
</tr>
<tr>
<td>5</td>
<td>Heart Rate</td>
<td>HR</td>
<td>The inverse of the time difference between two consecutive S (instantaneous heart rate)</td>
</tr>
<tr>
<td>6</td>
<td>Pulse Transit Time</td>
<td>PTT</td>
<td>The time difference between the R wave in the ECG and corresponding D</td>
</tr>
</tbody>
</table>

In [22], different morphologies of PPG pulses are represented (Fig. 4). When the PPG pulse exhibits two explicit local maxima (Fig. 4 (a)) as in the case observed in young healthy individuals, it is possible to extract several features involving the location of the second local maximum. However, the subjects' age enrolled in our study being relatively high (mean = 58.9 years - Table 1), PPG pulses we recorded did not generally possess two local maxima as these pulses were more similar to Fig. 4 (c-e). Thus, features related to the position of the second local maximum were not considered.
B- Reduction of the number of features

The time features in Table 2 (AC, CT, SV, RV, HR and PTT) were computed for each PPG pulse resulting in a considerable number of features. In order to avoid this inconvenience (curse of dimensionality), the following procedure was implemented.

The whole duration of phase 3 (4.5-minutes) was divided into eighteen fifteen-second time intervals. It was empirically observed that this length is adequate so as not to be highly affected by a single outlier feature and at the same time being able to track dynamic changes in the features during the whole 4.5 minutes. All six time-domain features were calculated for each PPG pulse during of the fifteen-second time intervals. We render $TF_i^j$ as the series of the calculated time-domain feature $i$ in the $j^{th}$ time interval, and $DTF_i^j$ as the series of the discrete first-order derivatives of $TF_i^j$ ($1 \leq i \leq 6$ and $1 \leq j \leq 18$). Finally, the statistical mean, standard deviation, form factor and amplitude density of each of the $TF_i^j$ series were computed. The form factor and amplitude density are defined in (3) and (4), respectively [23]. $\tau$ is the length of each time interval which is fifteen seconds.

\[
\text{Form Factor of } TF_i^j = \frac{\text{standard deviation of } DTF_i^j}{\text{standard deviation of } TF_i^j}
\]  
\[ (3) \]

\[
\text{Amplitude Density of } TF_i^j = \frac{\sum_{k=0}^{\infty} TF_i^j(k)}{\tau}
\]  
\[ (4) \]

Therefore, with 18 time intervals, 6 time-domain features and 4 statistical features, each subject is characterized by $18 \times 6 \times 4 = 432$ statistical time-domain features. This value is lower than the case where each PPG pulse was considered separately. Since working with a large number of features is impractical for diagnostic purposes, the “sequential floating selection” algorithm in [25] is used for feature selection.
C. Classification

The standard k-Nearest Neighbor classifier in [24] was used for the purpose of classification.

As mentioned in section ..., due to the need to increase the number of subjects in each class, groups of subjects were formed (Table 3). The rationale is that a plausible diagnostic classification strategy is to differentiate patients with no or mild CAD (who are less in need of invasive measures like angiography) from those with severe CAD (2VD and 3VD). Therefore, we have implemented two different classifiers (CLA\(_{(G1)}\)\(_{(G2,3)}\) and CLA\(_{(G1,2)}\)\(_{(G3)}\)) defined as per Table 4.

### Table 4: Definition of two-class classifiers. For definitions of Group 1 and Group 2, please refer to Table 3.

<table>
<thead>
<tr>
<th>Name of Classifier</th>
<th>CLA(<em>{(G1)})(</em>{(G2,3)})</th>
<th>CLA(<em>{(G1,2)})(</em>{(G3)})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class 1</strong></td>
<td>Group 1 ((N=21))</td>
<td>Groups 1 &amp; 2 ((N=32))</td>
</tr>
<tr>
<td><strong>Class 2</strong></td>
<td>Groups 2 &amp; 3 ((N=27))</td>
<td>Group 3 ((N=16))</td>
</tr>
<tr>
<td><strong>Total number of subjects</strong></td>
<td>(N = 48)</td>
<td>(N = 48)</td>
</tr>
</tbody>
</table>

D. Performance Evaluation

1- Training and test data

A common method for evaluating the results of a particular two-class classification process is to use a separate set of train and test data. The classifier is trained using the train dataset, and its performance in classifying the test dataset is reported. Since we did not have a large number of subjects in each group, we performed our two-class classifications by repeating the process of randomly choosing our train and test datasets known as Leave-One-Out (LOO) [26] which is explained in the following steps.

*Step 1 – Determine the minimum size of the two classes, and call it \(m\).*

*Step 2 – Chooses \(m\) members of the bigger class \textbf{randomly} in order to have two classes of size \(m\), which is essential while using a KNN classifier.*

*Step 3 – For \(i = 1, \ldots, m\) and \(j = 1, \ldots, m\) repeat the following loop \((m^2\text{times})\):*

  *i) Consider the \(i^{th}\) element of the first group and the \(j^{th}\) element of the second group.*

  *ii) Train the classifier using the \(m-1\) remaining elements in each of the two groups.*

  *iii) Classify the two elements using the trained classifier, and store the resulting ACC, Sn, Sp, and the F measures.*
Since the steps above involve random choosing of \( m \) samples from the bigger group, the above process was repeated for 300 times in each classification in order to account for all possible combinations. In the end, the mean and standard deviation of all the stored performance measures (defined in Section ...) are calculated to evaluate the classification process using a specific set of features.

2- Performance metrics

Using an extension of the confusion matrix (Table 5) for a 2-class classifier, the Precision (P) and Recall (R) parameters are computed for each of the \( m \) classes using the elements of the generalized confusion matrix \( C(i,j) \) [25].

<table>
<thead>
<tr>
<th>Decision</th>
<th>Class 1</th>
<th>Class 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( True Positive ) (TP)</td>
<td>( False Negative ) (FN)</td>
</tr>
<tr>
<td>Ground Truth</td>
<td>Number of class 1 members that are</td>
<td>Number of class 1 members that are</td>
</tr>
<tr>
<td></td>
<td>correctly classified as class 1</td>
<td>wrongly classified as class 2</td>
</tr>
<tr>
<td>Class 1</td>
<td>( False Positive ) (FP)</td>
<td>( True Negative ) (TN)</td>
</tr>
<tr>
<td></td>
<td>Number of class 2 members that are</td>
<td>Number of class 2 members that are</td>
</tr>
<tr>
<td></td>
<td>wrongly classified as class 1</td>
<td>correctly classified as class 2</td>
</tr>
</tbody>
</table>

Fig. 5. Confusion matrix for a two-class classification (\( m=2 \))

\[
P_i = \frac{C(i,i)}{\sum_{j=1}^{m} C(i,j)} \quad \text{for} \quad i = 1,2,\ldots,m \quad (9)
\]

\[
R_i = \frac{C(i,i)}{\sum_{j=1}^{m} C(j,i)} \quad \text{for} \quad i = 1,2,\ldots,m \quad (10)
\]

For a \( 2 \times 2 \) confusion matrix (\( m = 2 \)), it is easy to show that: \( P_1 = \frac{TP}{TP+FN} = Sn \) (Sensitivity), \( P_2 = \text{Specificity} \) (Sp), \( R_1 = \text{Positive Predictive Value} \), and \( R_2 = \text{Negative Predictive Value} \).

The F-measure [25] is another measure defined by taking the harmonic mean of the precision and recall. It is an array of the size of the number of classes whose elements are calculated as in (11).

\[
F_i = \frac{2R_iP_i}{R_i + P_i} \quad \text{for} \quad i = 1,2,\ldots,m \quad (11)
\]
Intuitively, the $i^{th}$ element of the mentioned F-measure evaluates the performance of the classifier in classifying the original class $i$’s elements. The total accuracy of classification (ACC) as defined in (12) provides our final perspective of the classification performance.

$$\text{ACC} = \frac{\sum_{i=1}^{m} C(i,i)}{\sum_{j=1}^{m} \sum_{k=1}^{m} C(j,k)}$$ (12)

Generally, a larger ACC means the superior the performance of the classification process. Nevertheless, the performance of the classifier regarding each one of the classes has to be satisfactory as well, i.e. the elements of the F-measure have to possess a high statistical mean and a low standard deviation.

Therefore the overall performance of the proposed classification process is assessed by three criteria respectively:

- the total classification accuracy (ACC),
- the statistical mean and standard deviation of the F-measure’s elements.

An effective feature is expected to possess a high classification accuracy (ACC) while having large and almost equal F elements. As only two-class classifications were considered in this work, the two elements of F were deemed effective if they showed an absolute difference of about 0.25.

IV. RESULTS

In order to assess the performance of our approach, two different sets of results are presented: the first one is based on the implementation of the classification using only one time-domain feature. As there are six such features (AC, RV, SV, CT, HR and PTT), six series of accuracy and F measures are reported.

The second approach is based on the selection of a subset of the time-domain features. It is expected that such a combination will result in a better overall performance of the classifier.

A. Classification Using Individual Time-Domain Features

Given the eighteen time intervals and the four statistical measures, the six time-domain features (i.e. SV, RV, AC, PTT, CT and HR) each result in $4 \times 18 = 72$ statistical measures. First, the feature selection algorithms were used for each of the time-domain features individually with a termination condition of reaching 15 statistical features. Table 5 shows the format employed to report these results, whereas the classification results for each of the above...
time-domain features is shown in Table 6. For both classifiers, results of the PTT feature shows
the best performance in terms of accuracy and F measure for the 2nd class.

| Table 5: Display format used in Table 6
| ACC (%) |
| F Measure of First Class (%) | F Measure of Second Class (%) |

| Table 6: KNN8 classification results (ACC and F measures) for each time-domain feature. The best results for each classifier are highlighted with a dark background. |
| Classifier | Time-domain feature |
| AC | RV | SV | CT | HR | PTT |
| CLA_(G1)_(G2,3) | 61.8 | 72.7 | 66 | 53.1 | 73.3 | 74.2 |
| 56.6 | 51.0 | 68.5 | 63.6 | 58.8 | 58.5 | 39.7 | 48 | 70.6 | 62.4 | 68.5 | 66.8 |
| CLA_(G1,2)_(G3) | 70.3 | 65.6 | 70.6 | 61.0 | 63.9 | 74.3 |
| 69.6 | 62.4 | 53.8 | 61.6 | 57.8 | 69.1 | 37.9 | 65.2 | 54.9 | 56.7 | 62.1 | 73.2 |

B. Classification Using a Combination of Time-Domain Features

To select the best subset of features, the “sequential floating selection” algorithm was implemented. Table 7 displays the features that were selected and their associated statistical measure. a classification accuracy of about 80%. Table 8 determines the types of the statistical features used in Table 7.

| Table 7: Statistical Measures used in Table 8 |
| Classifier Name | Selected Time-Domain Features | Number of Statistical Measures | Description of the Statistical Measures |
| CLA_(G1)_(G2,3) | RV | 3 | Form factor (8th and 17th time intervals) |
| | PTT | 2 | Form factor (17th time interval) |
| CLA_(G1,2)_(G3) | CT | 2 | Form factor (1st and 15th time intervals) |
| | HR | 2 | Form factor (3rd and 9th time intervals) |
| | PTT | 2 | Form factor (3rd and 10th time intervals) |
### TABLE 8: TWO-CLASS CLASSIFICATION RESULTS USING BEST TIME-DOMAIN FEATURES AND KNN8 CLASSIFIER

<table>
<thead>
<tr>
<th>Classifier Name</th>
<th>Utilized Time-Domain Features</th>
<th>Number of Statistical Features</th>
<th>ACC (%)</th>
<th>F1 (%)</th>
<th>F2 (%)</th>
<th>Sn (%)</th>
<th>Sp (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLA_(G1)_(G2,3)</td>
<td>RV, PTT</td>
<td>5</td>
<td>78.8 ± 4.7</td>
<td>72.8 ± 6.2</td>
<td>73.4 ± 6.3</td>
<td>78.3 ± 6.1</td>
<td>79.3 ± 6.2</td>
</tr>
<tr>
<td>CLA_(G1,2)_(G3)</td>
<td>CT, HR, PTT</td>
<td>6</td>
<td>81.5 ± 4.8</td>
<td>76.0 ± 4.8</td>
<td>76.8 ± 7.8</td>
<td>80.9 ± 4.2</td>
<td>82 ± 8.1</td>
</tr>
</tbody>
</table>

### V. DISCUSSION

This work demonstrated the possibility of predicting the degree of blockage through time-domain features defined on the finger PPG and ECG signals during the FMD test. The best results in terms of accuracy were obtained when one group consists of ... and the other group is formed of ... subjects. Labeling of the angiograms by three expert cardiologists allowed the determination of the exact CAD (ground truth). Two classifiers were introduced, using four and five time-domain features, respectively.

### TABLE 9: COMPARISON OF DIFFERENT NON-INVASIVE METHODS OF DIAGNOSING CAD (TO BE COMPLETED)

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of cases</th>
<th>Reported Results in the literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ECG [give all ref]</td>
<td>[1][6]?</td>
<td>Sensitivity: 25% to 71% depending on the protocol used. For patients with 2 or 3 artery blockage, exercise ECG has a sensitivity of 81% and specificity of 66%.</td>
</tr>
<tr>
<td>Ultrasound FMD [give all ref]</td>
<td></td>
<td>Accuracy of 61%. Sensitivity of 53%. Specificity of 69% in discriminating between subjects with and without artery blockage.</td>
</tr>
<tr>
<td>Proposed method (PPG-FMD)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One of the limitations of our study is the grouping of subjects with different condition into the same classes to circumvent the relatively limited number of subjects. This approach allowed us to split the 48 subjects who were recruited so that the number of subjects in each class varied from 16 to 32. Using this regrouping, two classifiers were formed with slightly different performance: accuracy of 81.5 % and 78.8 % respectively whereas other statistical measures were also comparable. Future studies will need to address this shortcoming by recruiting more subjects.

Although far from being perfect, we propose that a direct application of our approach is the implementation of an efficient triage system for scheduling coronary angiography. This technique is thought to be able to non-invasively determine patients at a greater risk of CAD which can assist in scheduling them for coronary angiography. Another related aspect is the
efficiency in terms of the possibility of reducing the number of normal coronary (NC) cases. In our set of randomly selected patients, an astounding 37.5% were found to have no artery blockage (18 subjects of the 48 recruited). Given the cost of this invasive procedure, any reduction in the number of angiographies will help ease the financial burden on the healthcare system.

Given the ease of recording of the PPG and the non-invasive nature of the FMD test, this diagnostic method will be much safer and simpler compared to invasive angiography. In addition, PPG-FMD is superior to ultrasound FMD due to a less skilled-operator demanding procedure resulting in a much simpler and convenient implementation.

ACKNOWLEDGMENT

This work has been funded by the Iranian National Science Foundation (INSF) grant number 87041735.

REFERENCES


[18] Tehran Heart Center (THC), http://thc.tums.ac.ir/En/


