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A Hybrid Approach for Screening Endothelial Dysfunction using Photoplethysmography and Digital Thermal Monitoring

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***Abstract*—Cardiovascular diseases(CVDs) are the world's leading cause of death. Endothelial Dysfunction is an early stage of cardiovascular diseases and can effectively be used to detect the presence of the CVDs, monitor its progress and investigate the effectiveness of the treatment given. This study proposes a reliable approach for the screening of endothelial dysfunction via machine learning, using features extracted from a combination of Plethysmography, Digital Thermal Monitoring, biological features (age and gender) and anthropometry (BMI and pulse pressure). This case control study includes 55 healthy subjects and 45 subjects with clinically verified CVDs. Following the feature engineering stage, the results were subjected to dimension reduction and 5-fold cross-validation where it was observed that models Logistic Regression and Linear Discriminant provided the highest accuracies of 84% and 81% respectively. We propose that this study can be used as an efficient guide for the non-invasive screening of endothelial dysfunction.**

***Index Terms*—Endothelial Dysfunction; Non-invasive Assessment; Photoplethysmography (PPG); Digital Thermal Monitoring(DTM); Cardiovascular Disease (CVD)**

I. INTRODUCTION

World Health Organization (WHO) states that Cardiovascular Disease (CVD) is the leading cause of death under the age of 70 years [1]. Since the primary disorder affects the arteries CVDs manifests as coronary heart disease, cerebrovascular disease, congenital heart disease, deep vein thrombosis, pulmonary embolism or many other heart conditions [2].

In recent years, there has been a renewed focus on preventive strategies, including screening to detect the disorders at an early stage. This has lead to the recognition of a close correlation between CVDs and the vascular health of individuals [3] [4] [5]. Early detection of the former could therefore pave the way for drastically reducing the premature mortality from CVDs [1].

The endothelium is a one-cell thick layer lining the innermost surface of the entire cardiovascular system from the heart to the smallest of capillaries. Endothelial Dysfunction (ED) could be considered as a vascular disease which occurs due to the presence of cardiovascular risk factors such as high blood cholesterol, high blood pressure, insulin resistance, excessive alcohol consumption, smoking, lack of exercise, obesity, poor diet and genetics [2] [6]. ED can also be highlighted as the first stage of cardiovascular diseases and thus, an accurate and efficient approach to detect CVD before it progresses into complications [7].

Several invasive and non-invasive methods have been introduced in recent years for the detection of ED. While Coronary Angiography serves as the gold standard for the invasive detection method of ED it has some evident drawbacks such as; the involvement of complex procedures, high time consumption, risk of infection and vascular injury [8]. Hence, non-invasive techniques such as Flow Mediated Dilation (FMD), Peripheral Arterial Tonometry (PAT), Photoplethysmography (PPG) and Digital Thermal Monitoring (DTM) are considered as more fitting techniques. Despite being widely used non-invasive assessment techniques FMD and PAT have several impediments such as their high cost, reproducibility and dependency on the operator [9] [10]. Thus, PPG and DTM are considered as the most emerging approach for the evaluation of ED.

PPG measures the variations in blood flow within microvascular tissue by utilizing the transmission or reflection of an Infrared or Red light. This is possible due to the high absorption of light in blood in comparison with the surrounding tissue. Therefore, PPG is considered a good indicator of endothelial dysfunction and stiffness in blood vessels [11] [12].

The evaluation of ED using DTM is conducted alongside the context of Reactive Hyperemia (RH). RH is the sudden increase in the perfusion following the brief interval of ischemia, occlusion of the blood. This is an important function of a healthy vasculature where the proper RH corresponds to the good ability of autoregulation of an individual. Digital Thermal Monitoring is a non-invasive measurement of body temperature mainly focused on assessing vascular reactivity. In this case, there exist a rise in the DTM signal due to the temporarily elevated blood volume from releasing the occlusion and a gradual decrease following the washout of the vasodilators [13] [14] [15] [16] [17] [18].

In previous works, one study has investigated the relationship between the PPG with ED [19] where they have identified features that are in correlation with the said vascular injury. Furthermore, they illustrate the basic distinctions of PPG waveforms, the most commonly seen artifacts integrated with the acquired PPG signals and the relationship between the PPG indices to non-communicable conditions such as hypertension, diabetes, cardiovascular disease, vascular aging

This research was conducted under the ethical approval of Ethics Review Committee,Faculty of Medicine, University of Colombo, Sri Lanka (Ethics Review Number: EC/18/208)

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and arterial stiffness. However, they have concluded the study at the feature extraction stage and have not focused on the diagnosis of CVD.

Another group of researchers has focused on the analysis of PPG with ED where they have proven the two hypotheses; the capability of a machine learning (ML) approach to screen ED using PPG features and the ability to improve the said classification using the subject anthropometric features [9]. They have achieved a classification accuracy of 71% and a recall of 67% and have chosen Support Vector Machine (SVM) as their choice of the classifier. Nonetheless, the group plans to extend the study with an exploration of a larger dataset where it currently compromises a relatively smaller dataset of 59 subjects.

Some experimentation has explored the relationship between the ED and DTM signals where vascular function and the sudden rise in temperature trailing an occlusion of blood flow have been analyzed [13] [14]. One study has generated a simulation of thermal response of a fingertip to blood flow rate during RH and has analyzed the variation of the DTM waveform with respect to its morphology, time delays and temperature variations and have assessed the sensitivity of each of these indices to RH [13]. As a result they have identified Temperature Rebound (TR) and Finger start temperature; skin temperature (Tss) as the most significant parameters to assess RH. Another research has discussed the generation of the Zero Reactivity Curve (ZRC) and has further proven the significance of Vascular Reactivity Index (VRI); adjusted Temperature Rebound (aTR) to the evaluation of endothelial function [14].

Furthermore, some researchers have focused on the combination of DTM and Peripheral Arterial Tonometry (PAT) technologies and have scrutinized their correlation to ED through a statistical analysis [20] [21]. They have identified the DTM indices such as Temperature rise and fall rates and Area Under the Curve (AUC) and PAT Reflection Index as most sensitive to ED. However, the classification has been done on subjects with and without diabetes and the specific conditions of the vascular system have not yet been investigated.

This paper proposes an in-detailed evaluation of ED using a combination of signals from PPG and DTM for the first time where it extends the previous studies which are solely based on either PPG or DTM technologies. This also overcomes the problems seen with PAT due to its considerable sensitivity towards motion, high cost and lack of availability in global context [22]. Furthermore, this study contains a substantially reliable approach to classify the subjects suffering from ED not only through the sequence of bio-signals but also based on the consideration of the anthropometric features of the subject. This leads to the provision of accurate results to a diverse demographic. Hence this research can also be recognized as the first research of using PPG,DTM and anthropometric features together for ED evaluation. Through the combination of these features, we hope to validate the hypotheses that this consolidation has higher accuracy, sensitivity and specificity levels in comparison with the other similar studies in its ability to assess ED.

II. METHOD

A. Data Collection Procedure

The data collection program, under the ethical approval (Ethics Review Number: EC/18/208) from the Ethics Review Committee (ERC) of the Faculty of Medicine, University of Colombo, was conducted in Asiri Surgical Hospital, Colombo 00500. The dataset contains 100 samples (age range:20 to 60 years, male: female of 56:44) of 55 healthy subjects and 45 subjects having risk factors for CVD. A structured questionnaire was used to gather data on the medical history, daily dietary and exercise habits and the existence of CVD risk factors such as; hypertension, diabetes and hyperlipidemia. A consultant cardiologist concluded the existence of ED conditions in each subject. Prior to the signal acquisition procedure, the participants were requested to refrain from eating, smoking, alcohol consumption and taking medications for at least 6 hours. They rested for 30 minutes and were kept in the supine position for 15 minutes.

The PPG signals were taken using a Pulse Oximeter probe, which utilizes both Infrared and Red channels and a thermal sensor was used to acquire the DTM signals. The PPG and DTM probes were attached to the index finger and middle finger of each hand of the subject respectively. The baseline signals were recorded for 3 minutes which was then followed by the recording of signals during the occlusion of a pressure cuff around the right brachium for 5 minutes. Finally, the signals after the deflation of the cuff were acquired for another 7 minutes. Throughout the process, the subjects remained in the supine position with closed eyes and minimum possible movement to reduce the occurrence of motion artifacts in the bio-signals.

B. Preprocessing

The signal processing techniques mentioned in the patent [23] by the same research group were used for PPG based identity pulse generation.

The raw signals acquired were immediately followed by a thorough preprocessing stage to denoise the signals. The implementation of the digital filters used in the preprocessing stage, the feature calculation using PPG and DTM signals in the feature engineering stage and the training of machine learning algorithms were conducted using MATLAB software (The MathWorks, Inc., Natick, MA, USA).

The acquired signals were analyzed in both time and frequency domains and the powerline interferences were removed via Butterworth notch filters. The PPG signals were then subjected to a two-stage wavelet filtering of bior1.5 level 16 and db10 level 16 for further denoising and elimination of motion artifacts respectively.

Initially, the acquired DTM signals compromised of considerable noise. In contrast to the thermal signal processing technique used in [23], a different preprocessing method was used as follows. Each signal was sent through an intensive pre-processing procedure of outlier removal, median filtering and piecewise smoothing where each piece of the signal was filtered using a Savitzky-Golay filtering. Finally, all partitions were combined using the modified Akima (Makima) interpolation.

C. Feature Extraction

Following the preprocessing of the PPG and DTM signals, the signals acquired need to be studied to extract the signal properties that correlate with the aimed classification. The purpose of this study is to emphasize the classification accuracy gain after combination of features from two bio-signal domains. Therefore, most of the features considered in this research were validated in previous studies.

1) PPG Feature Extraction: A single PPG pulse consists of 2 phases; the anacrotic phase with the rising edge corresponds to the systolic state of the cardiac cycle and the catacrotic phase with the falling edge represents the diastolic state. The notch is commonly known as the dicrotic notch pin-points the closing of the aortic valve and has proven to be an important indication of endothelial health.

Additionally, the first derivative of the waveform; Velocity Plethysmogram (VPG), or the second derivative waveform; Acceleration Plethysmogram (APG) also provides many significant features for the indication of ED. The APG waveform consists of four indicative waves; a (early systolic positive wave), b (early systolic negative wave), c (late systolic re-increasing wave), d (late systolic re-decreasing wave) and e (early diastolic positive wave) [19] and the heights of these waves hint the endothelial function of an individual.

The overall features from PPG signals were obtained either directly from the PPG waveform or the VPG waveform or the APG waveform. Additionally, spectral indices were also integrated into the PPG features [9] [19]. Fig.1 illustrates PPG, VPG and APG waveforms with the parameters used in the calculation of features. Table I. depicts the features obtained using PPG signals and a summary of their significance.

2) DTM Feature Extraction: The DTM signals were analyzed under the context of RH which includes three main partitions; the baseline signal acquired in the resting stage, the DTM signal under the occluded state and the DTM signal after the deflation of the pressure cuff [13] [18]. Following the occlusion of the pressure cuff, the temperature of the measured site drops due to the lack of blood flow. This negative peak is named the Nadir's peak and is used in the calculation of many DTM features correlating ED. Then the deflation of the pressure cuff causes a sudden rise in the temperature resulting in a spike of temperature called the 'temperature rebound'.

In addition to the DTM signal curve, the DTM feature extraction procedure involves the generation of Zero Reactivity Curve (ZRC) which depicts the variation of the subject's temperature if there exists no vascular reactivity to RH [14] [17]. This curve acknowledges the baseline

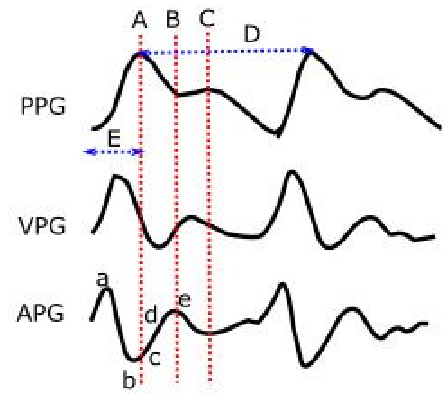


Fig. 1. PPG, VPG and APG waveforms and the significant parameters related to ED whereas A, B, C, D, E represent the systolic peak, dicrotic notch, diastolic peak, peak to peak interval and crest time respectively and a,b,c,d,e are the indicative waveforms of the APG waveform.

TABLE I
PPG SIGNAL FEATURES AND THEIR REPRESENTATION

Feature	Significance
Systolic Amplitude	The pulsatile changes in the blood volume. This relates to the stroke volume and the local vascular distensibility [24] [19].
Peak to Peak interval	The interval between two consecutive systolic peaks. This also depicts the full cardiac cycle [19].
Pulse Width	The width of the PPG pulse. This is determined at the height equal to half of the systolic amplitude and is a good indicator of the systolic vascular resistance [25] [19].
Pulse Area	The total area under the curve of the PPG pulse [19].
Crest Time	The interval between the foot of the PPG pulse to the systolic peak [19].
Augmentation Index (AI)	The effect of the wave reflection on the arterial systolic pressure. The early return of the reflected waves due to decreased compliance of the blood vessels can be detected using this index [19].
Stiffness Index (SI)	The stiffness in the subclavian artery. The height of the subject is said to be proportional to the time taken for the blood to travel from the root of the subclavian artery to the site of measurement. This is equal to the interval between the systolic peak and the diastolic peak [26] [19].
Ration b/a	Represents arterial stiffness and distensibility [27] [19]. This positively correlates to the Framingham risk score, a popular method used to estimate CVDs [28].
Ratio c/a	Represents decreasing arterial stiffness [19].
Ration d/a	Represents left ventricular after-load and arterial stiffness [19].
Ratio e/a	Represents arterial stiffness [19] [29].
Ratio (b-c-d-e)/a	Represents potential risk of atherosclerosis and vascular aging [19] [30].
Ratio (b-e)/a	Alternative for Ratio (b-c-d-e)/a in cases of absent c and d points [19] [30].
Ratio (c+d-b)/a	Represents vascular aging [19]
PPGi (Spectral index 1)	Sum of the amplitudes of the first three peaks in frequency domain
PPGVLFi (Spectral index 2)	Amplitude of first peak/PPGi

TABLE II
DTM SIGNAL FEATURES AND THEIR METHOD OF CALCULATION

Feature	Calculation
Temperature Rebound (TR)	The difference between the maximum temperature after the deflation of the cuff and the baseline signal temperature [13] [14] [15].
Nadir Peak (NP)	The difference between the maximum temperature after the deflation of the cuff and the minimum temperature after the occlusion of the cuff [13].
Time to Temperature Rebound (TTR)	The interval between the NP and the TR [13].
Area Under the Curve (AUC)	Area under the DTM signal curve within the time period of NP to TR [13] [15].
Finger start temperature (Tss)	Equals to the skin temperature at the baseline signal acquisition.
Adjusted Temperature Rebound (aTR)	The maximum value of the Reactivity curve (RC). RC refers to the difference between the DTM signal after deflation and the ZRC [14] [17] [31].
Maximum of the slope(RC)	Maximum value of the slope of the RC curve.
Area under the Reactivity Curve	Total area under the RC.

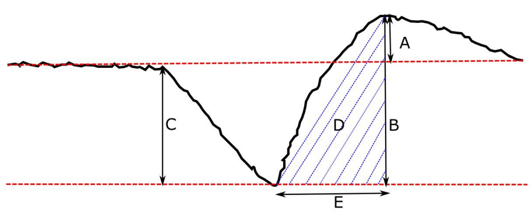


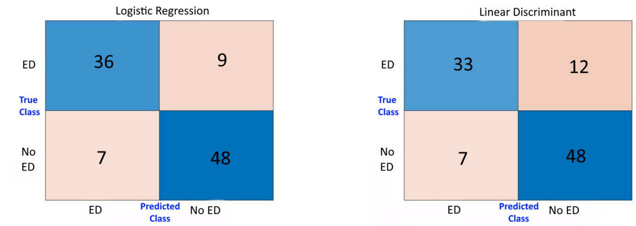
Fig. 2. DTM waveform during the resting state, occluded state and deflated state and significant parameters related to ED whereas A, B, C, D, E represent Temperature rebound, Nadir to peak, Baseline temperature, Area Under the Curve and Time to temperature rebound respectively.

temperature of the subject, room temperature and the slope of the temperature fall during the occlusion. A total of 8 features including the skin temperature of the finger which was measured during the test were extracted after studying the DTM morphology. Fig.2 demonstrates the parameters and features calculated using the DTM signal. Table II. represents the DTM features and their method of calculations.

3) Anthropometric Features: Recent studies have observed that PPG signal morphology displays variations based on certain biological and anthropometric features of each person [9] [32]. Thus, trailing the completion of feature calculation using PPG and DTM signals, the obtained feature set is then integrated with 4 anthropometric features collected from each subject; gender [33], age [34], pulse pressure [35] and BMI. Therefore, the algorithm was accustomed to obtain considerably accurate predictions even for diverse demography.

D. Dimension Reduction and Classification

After obtaining the combination of 28 features from the PPG, DTM signals and individual anthropometry, it is vital to distinguish the features that are most significant for the aimed classification. Thus, three phase model training was



(a) (b)

Fig. 3. Confusion matrices for Logistic Regression (a) and Linear Discriminant (b)

conducted with PPG based features, DTM based features and combination of PPG,DTM and anthropometric based features. Further to this, after the normalization of the extracted features, they were subjected to dimension reduction using Principal Component Analysis (PCA). The PCA was used as a dimensionality reduction technique during model training and prediction. Obviously, PCA does not reduce the number of features to be obtained at the time of feature extraction, but what is fed to the model. With PCA, the original feature set of 28 features was reduced to 12 components where it was observed that 90% of the total variance is contained within them.

The reduced features were then subjected to 5-fold cross-validation to avoid over-fitting of the classification model which occurs when trained and tested on the same dataset. Finally, 23 classification models in MATLAB were trained with the reduced features and the accuracy of each model was tested along with some performance evaluation parameters in machine learning.

III. RESULTS AND DISCUSSION

The dataset used for the training of the classification models consists of 55 healthy subjects and 45 subjects with ED. The training of the classification models was conducted subsequently to the 5-fold cross-validation which uses each sample in both train and test sets in different trials. Hence, this separation of test and train sets successfully avoids the over-fitting of the classification model to the given set of data. The reason behind the selection of cross-validation over hold-out validation is because of the comparatively smaller number of samples for which the classification was performed. In cases of smaller datasets, the application of hold-out validation results in the training of classifiers which are heavily biased on the seed of the partition; the split of the train and test datasets at that specific moment.

The ML models supplied with MATLAB are derived on relatively simple SVM, KNN, Tree, and Regression methods compared to deep learning models. The simplicity of the models provided, approximately balanced binary samples and the above mentioned k-fold cross validation led to select a better performance model even with a relatively small dataset. It was observed that the machine learning models Logistic Regression (LR) and Linear Discriminant (LD) obtained the highest accuracy values for the classification of

TABLE III
A COMPARISON OF THE ACCURACY, SENSITIVITY, SPECIFICITY, PRECISION, RECALL AND F1 SCORE VALUES BETWEEN LR AND LD.

	LR	LD
Accuracy	84.0%	81.0%
Sensitivity	80.0%	73.3%
Specificity	87.3%	87.3%
Precision	83.7%	82.5%
Recall	80.0%	73.3%
F1 score	81.8%	77.6%

subjects with and without ED. Moreover, apart from the top 2 models Ensemble Subspace Discriminant, Ensemble Bagged Trees and Cosine K-Nearest Neighbour (KNN) obtained the highest accuracies respectively. Fig.3 illustrates the confusion matrices obtained for the models with the highest accuracies; LR and LD. Table III. summarizes the confusion matrix values into accuracy, sensitivity and specificity figures.

Even though the currently utilized dataset remains approximately balanced with healthy and diseased (with ED) subjects, for extended verification of the algorithm parameters such as precision, recall and F1 score was calculated. This is due to the usefulness of the F1 score in indicating a more authentic representation of the classification models in the case of uneven distribution. As indicated in Table III. LR has obtained the highest values for precision, recall and F1 score.

It is important to note that due to the application of cross-validation the evaluation parameters given in the previous sections display slight variations with the different partitions of the dataset and thus, Table III. is a representation of the average values of multiple iterations of the machine learning algorithm.

As clearly seen in Table IV. PPG and DTM based features in separation generate low accuracy models in contrast to the models derived by the combination of PPG, DTM and anthropometric features.

The dimension reduction using PCA was conducted to eliminate the redundancy due to the features correlated with each other. Such superfluous features can lead to a decline in the accuracy of the classification due to misleading the classifier being trained. Prior to this stage, all features of the original matrix were normalized in order to assign equal standard deviations and thus, the same weightage was given to all features for which PCA is calculated.

As more than 90% of the total variance of all features remain within the most prominent 12 Principal Components (PCs) it can be deduced that these components are an adequate representation of the overall original feature matrix with high dimensionality. The results in Table IV. further justifies the selection of 12 principal components over other approaches such as; no application of PCA, selection of 14 components containing 95% of total variance and selection of 8 components containing 80% of the total variance.

When analyzing the obtained results it can be observed that the model LR surpasses the other classification models in all the evaluation parameters considered. Moreover, it displays a 3% raise with respect to the model with the second-highest accuracy; LD.

TABLE IV
ACCURACY COMPARISON OF CLASSIFICATION MODELS

Model	PPG Only	DTM Only	PPG+DTM Without PCA	8 PCs (80% Var.)	12 PCs (90% Var.)	14 PCs (95% Var.)
Logistic Regression (LR)	63.0%	59.0%	68.6%	81.7%	84.0%	75.0%
Linear Discriminant (LD)	62.0%	58.0%	-	83.0%	81.0%	79.0%
Ensemble Subspace Discriminant	66.0%	58.0%	77.7%	83.0%	78.0%	80.0%
Ensemble Bagged Trees	57.0%	58.0%	78.7%	76.3%	76.0%	74.0%
Cosine KNN	53.0%	55.0%	77.7%	82.0%	76.0%	70.0%
Linear SVM	51.0%	58.0%	78.0%	79.3%	79.0%	80.0%
Coarse Tree	51.0%	57.0%	79.3%	76.3%	76.0%	70.0%

IV. CONCLUSION AND FUTURE WORK

This is the first attempt of using a combination of PPG, DTM and anthropometric based features for detecting ED to the best of our knowledge. The accuracy(84%), sensitivity(80%) and specificity(87%) values obtained from the classification using the Logistic Regression model confirm that the proposed combination of PPG and DTM signals along with the subject anthropometry, provides an assessment of ED of considerable accuracy when considering consultant cardiologist's diagnostic opinion of ED as the baseline. By considering PPG and DTM based features as a whole, we can build up strong classifiers for ED detection than that of the weak classifiers built separately. This combination also produces meticulous results to a wider demographic due to the additional consideration of subject anthropometry.

The utilized dataset contains samples of 55 healthy subjects and 45 subjects with ED. Therefore, with higher number of samples it could be assumed increased sensitivity and accuracy figures. Additionally, a dataset with more samples would pave way for much complex machine learning methods such as a Neural Network to be implemented which has the potential to further boost the accuracy of the classification. For future extensions of this work, the validation of this method using a more commonly used clinical diagnostic examination such as the infusion of vasoactive agents is suggested. Likewise, due to the effect of skin color on the IR transmission in PPG, the integration of consideration of each subject's skin complexion into the signal processing algorithm would elevate the practical applicability of this approach in the global context.

In conclusion, the approach proposed in this study to screen ED using the non-invasive signal acquisition of PPG and DTM with the subject's anthropometry proves to be a considerably accurate and lucrative avenue for the future of medical diagnosis.

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