

Towards Phenotyping Suppressed Anger in Perimenopausal Women with Lyfas Biomedical Application: A Comprehensive Diagnostic Reliability Study

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Abstract: Biomedical applications are gaining popularity in decoding human emotion. Anger causes sympathetic overdrive and is a normal emotion, which is either expressed or kept suppressed. Suppressed anger (SA) is a major health issue often causing serious cardiometabolic and mental diseases due to cardiac autonomic neuropathy (CAN), where the sympathovagal homeostasis is compromised to compensate for it. Lyfas is a smartphone-based biomedical application that captures CAN through short (120 sec) heart rate variability (HRV) and its associated cardiovascular optical biomarkers (COBs). This paper attempts to diagnose SA with the help of Lyfas COBs and a few important physical parameters in a cohort of Indian perimenopausal women (N=415; case 205 and control 210), who suffer from mood dysregulation due to the depletion of natural estradiol (E2) in the brain. The clinical Anger Scale (CAS), a gold-standard anger assessment tool is taken into consideration as a reference scale. The strength of correlations of each COB and physical parameter with CAS and its reliability is calculated using Spearman's correlation and Bland-Altman's reliability assessment, respectively. The paper concludes that COBs such as SDNN, RMSSD, and LF/HF along with physical parameters (BMI) are hallmark biomarkers for SA phenotypes with 71% of accuracy, 74% of j-statistics, as well as 92% of precision. Early diagnosis of SA with Lyfas would facilitate early treatment, and thereby improve the quality of life.

Keywords: Anger phenotyping, Lyfas, Suppressed anger, Mobile health, Mental health.

KEY MESSAGE

Early anger phenotyping using Lyfas, a smartphone-based cardiovascular optical biomarker (COB) application could elevate the quality of life by preventing anger-induced adverse biopsychosocial consequences. This comprehensive study observes that COBs, such as low SDNN and RMSSD, and high LF/HF scores in the Lyfas analytics are the reliable hallmark of expressed and suppressed types of anger. Obesity also plays a significant role in anger response. Early diagnosis of anger eases early anger management and hence improves the quality of life.

INTRODUCTION

Mental health has been revisited with utmost importance in the corona mayhem. Assessment of mental health is therefore a need to screen, diagnose, and treat the disorders. Questionnaire-based tools are still the mainstay of screening, diagnosing, and grading a mental illness. There are specific mental health questionnaires for diagnosing and grading specific

mental illnesses. These tools have the limitations of human bias due to deliberate falsification or misinterpretations of the questions or answers by the test-takers or interpreters. During the corona pandemic, meeting a psychiatrist has been a challenge due to several administrative mandates. Hence, on 25/3/2020, Govt. of India legalized the telemedicine model of healthcare delivery with guidelines, where patients and medical doctors can communicate with each other online maintaining certain protocols and stipulations [1].

Phenotyping is a method of determining the characteristics based on observational or exhibiting traits. Anger is a protective emotion until it becomes uncontrolled. It can be of expressed or suppressed form, based on the extent of autonomic nervous system (ANS) involvement. Anger outburst is seen associated with sympathetic overdrive, while the parasympathetic system tries to buffer it. During the corona pandemic, obstructed social interactions, a chaotic socio-economic state, an uncertain future, a high incidence of virus-related morbidity and mortality, and several restrictive administrative mandates have caused anger in the population, as found in the work of Smith *et al.* (2021) [2]. While, expressed anger (EA) is more prevalent in men as found in the research of Leonard (2020) [3], suppressed anger (SA) is more

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prevalent in women as a good number of perimenopausal women complain of intractable SA episodes, as shown in the study of Suh *et al* (2021) [4] due to various biopsychosocial adversities associated with them. SA is an atypical state of anger emotion, when the anger outburst does not take place but stays inside the person for a longer period, compared to EA. Women have better compensatory mechanisms in the brain and therefore do not usually express anger as men do. Apart from the environmental factors, the anger trait has a genetic basis through the expression of the monoamine oxidase (MAO)-A gene, as found in the study by Mentis *et al.* (2021) [5], endocrine irregularities *e.g.*, oestradiol (E2) and progesterone depletion, mentioned by Denson *et al.* (2018) [6] and Chattopadhyay (2012) [7], substance abuse described by Lesser (2021) [8], several other environmental factors shown by Doyle *et al.* (2021) [9], and mental illnesses that show high grades of anger issues are mentioned in the study of Roy *et al.* (2020) [10]. The neurophysiology of anger shows that the orbital, medial, and ventrolateral frontal cortex are the key brain regions concerned with anger response and hence emotion tagged with anger is expressed more in these regions, as shown in the work of Blair (2012) [11]. EA is due to an aberration in the amygdala-hypothalamus-periaqueductal grey matter [11]. The authors of this paper hypothesize that SA is a balanced form of EA, found in women. However, if untreated, SA often leads to serious cardiovascular diseases, such as the risk of heart attack as the longitudinal study of Vella *et al.* (2021) has shown [12].

Emotion decoding by biomedical applications using digital signal processing is gaining popularity in today's cutting-edge digital healthcare. Smartphone-based applications are of choice due to the increased number of smartphone users, cheaper mobile data, patient-centric delivery, higher version of data privacy, and pervasive nature of the healthcare delivery modes [13]. It's a new industry and the estimated market size will be \$213.6 billion by 2025 from \$50.8 billion in 2020 at a CAGR of 33.3% [13]. Using the optical sensor of the smartphone's rear main camera and the in-built light source, these can measure the flow and volume of the capillary blood in the index finger, when it is gently pressed on the camera [14]. The principle is called arterial photoplethysmography (APPG). Using the principle of APPG, photochromatography, and digital signal processing capillary signals such as Pulse wave velocity (PWV) and Pulse rate variability (PRV) are captured and analyzed [15]. PRV is synonymous with

Heart rate variability (HRV). HRV and its related cardiovascular optical biomarker (COB) correlate as a surrogate for the Cardiac autonomic modulation (CAM) of the heart, which in turn gives a measure of the state of the mind-body homeostasis. *Lyfas* is not only such a smartphone-based optical biomarker instrument, it is a quantum digital health platform containing several mental health instruments and tools that anybody can use at any time from anywhere [15]. The instruments help measure the sign symptoms and the corresponding score, while the tool helps in clustering/classification of the state-of-the-art mental health [15]. Its proprietary AI-ML algorithm gives downloadable mind-body analytics of the test-takers in just five minutes. *Lyfas* has been used in screening subclinical depression in the vulnerable population with its cascading other mental health effects such as insomnia and negative thoughts [16], mental health issues such as anxiety, stress, and depression during the corona period [17].

The *objective* of the study is to phenotype SA in Indian perimenopausal women using *Lyfas* as the early diagnostic tool. Early detection of SA could prevent related health issues and thereby, improve their quality of life. These women reported frequent SA-related issues to the authors during the corona time.

The *novelty of the study* lies in that anger phenotyping with COBs has never been attempted so far to the best of the knowledge of the authors. In this comprehensive and cutting-edge research, using *Lyfas*, an attempt has been made to investigate the anger trait in perimenopausal women who suffer from various biopsychosocial stress during this phase of life [18].

MATERIAL AND METHODS

A. Ethics Clearance

The study protocol was approved by the Vagus Institutional Ethics Committee, Bengaluru, Malleswaram, Karnataka, India review board, which is registered with the Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, Govt. of India (No. ECR/1181/Inst/KA/2019, dated 30-01-2020) [19].

B. Patients' Consent

Signed informed consents of all participants' have been taken on the organization letterhead according to the *declaration of Helsinki* by the research team prior test [20].

C. Study Design

Coding and Computation

Computations are done using Python 3.9.8 (64-bits) on IDLE editor in Windows 10 OS.

Perimenopausal Condition Check

All subjects are web-enrolled and the signs and symptoms are examined by two senior gynecologists having an average experience of 20 years. Key signs and symptoms considered in this work are – (i) irregular menstruation (onset, duration, and flow), (ii) hot flush, and (iii) mood swings (stress, anger-anxiety, and depression or SAAD) as mentioned by Du *et al.* (2020) [21]. Subjects with these conditions over the *previous 6 months* are recruited for the study.

Clinical Anger Scale (CAS)

CAS is a gold-standard screening and grading instrument, developed by Snell *et al.* (1995) which is reliable. [22] It has 21-items each with a four-point scale (0, 1, 2, 3). The sum of the scores gives the total score for the subject. Overall, there are four grades based on the CAS scores as (i) Minimal (score: 0-13), (ii) Mild (score: 14-19), (iii) Moderate (Score: 20-28), and (iv) Severe (Score: 29-63). [23] In this paper, CAS scores are the '*dependent*' variables or *responses*, which are divided into four groups of CASs, mentioned below.

Lyfas

Lyfas is a novel smartphone-based, and non-invasive optical biomarker capturing tool. The tool has been developed using the principle of digital signal processing [24]. It can capture a total of 101 different digital biomarkers and is commercially available. These functional biomarkers are indicative of the psychophysiological state of an individual [24]. *Lyfas* works on two principles, photoplethysmography (PPG) and photochromatography (PCG). PPG measures blood volume changes in the microvasculature, while PCG measures the reflected light from various blood components such as cells and solutes [24]. The process is carried out using an optical sensor on the camera and its flashlight acting as an information capturing layer [24]. The next layer is a signal processing layer, which consists of the proprietary mathematical modeling and algorithms (a combination of heuristics-ML-AI), which converts the input signal into actionable metrics, which in turn captures the functional biomarker parameters system-wise [24]. These parameters were then validated in clinical settings (history, physical examination, and laboratory

investigations) to detect several electromechanical and physiological activities, such as cardiovascular mechanics, hemodynamic, hemorrheology, indicative hematology, and biochemistry in the test takers [24]. The study by Das and Chattopadhyay (2021), *Lyfas* has also been found reliable in predicting the cardiac risks in (i) Duchenne muscular dystrophy [25] and (ii) Chronic Obstructive Pulmonary Disease (Chattopadhyay and Das (2022))[26]. In another study by Chattopadhyay and Das (2022), *Lyfas* has also been found reliable in phenotyping the triad of hypertension-anger-anxiety in a vulnerable adult sample [27]. A sample *Lyfas* analytics snapshot can be seen in Figure 2.

In this aspect, it is worth noting that *Lyfas* can give a psychobiological snapshot of the body. Despite, anger is not expressed, the COBs, can assess the state of anger, be it the SA, in the body and work as a clinical biomarker for SA diagnosis.

The *working principle of Lyfas* has been elaborated step-by-step as follows:

Step-1: Placing the index finger and lightly pressing on the rear main camera of the smartphone with the Android version 7 and above operating system, pre-loaded with *Lyfas* application

Step-2: Relaxed position with normal breathing and start the test after ticking the consent box and then follow the voice-guided steps of the test

Step-3: The camera light captures the capillary blood volume using the principle of Photoplethysmography (PPG), Arterial photoplethysmography (APPG), Photo chromatography (PCG), short Heart Rate Variability (120 seconds HRV), Mobile Spirometry (SPM), and Manoeuvres like Orthostatic homeostasis to extract 101 clinically established digital biomarkers

Step-4: Grouping of biomarkers into various organ systems using its proprietary heuristics, ML, and finally AI algorithm

Step-5: AI-enabled analytics of these biomarkers to assess several psychophysiological states of the body and visualization, and finally

Step-6: Correlating analytics with clinical conditions.

Rationale of Parameter-Selection

HRV and its correlated COBs are surrogates for cardiac autonomic modulation (CAM) to maintain psychophysiological homeostasis and hence are a

battery of potential markers of cardiac autonomic neuropathy CAN. External stimuli may cause CAN by disturbing the 'sympathovagal' balance of the heart. Here, the increased sympathetic drive is reflected through high LF/HF and SD2/SD1, low pNN50, RMSDD, SDNN, which may be noted in the disorders with high sympathetic drive, e.g., generalized anxiety disorders [28], schizophrenia [29], obsessive-compulsive disorders [30], bipolar disorders [31], and in many other illnesses. A relatively elevated parasympathetic drive is evident in severe degree depression, where the sympathetic drive lowers but the parasympathetic drive remains unaltered [32].

On the other hand, *physical parameters*, such as middle-Age, raised HR (evident by palpitations due to increased vasomotor response to hormonal imbalance [33]), BMI (gained weight towards obesity [34]), high systolic and diastolic BP (as essential hypertension settles in the body as age advances [35]), irregular synthesis and secretion of estradiol and progesterone (which is a measure of the hypothalamus-pituitary-ovarian axis [36]), TSH (often is elevated to compensate for the increased demand of thyroxin in the body [37]), HbA1c (rises as type-2 diabetes settles down in the body [38]), and cortisol (a measure of the hypothalamus-pituitary-adrenal axis is often elevated due to the increment of stress [39]) have direct or indirect relationships with the perimenopause stage in the women's life.

Optical biomarkers (SDNN, RMSSD, pNN50, SD2/SD1, and LF/HF), obtained by the Lyfas test and *physical parameters* (Age, HR, BMI, systolic and diastolic BP, estradiol, TSH, HbA1c, and cortisol), obtained by the laboratory test and physical examination are the '*independent*' variables or *factors*. Statistically significant ($p < 0.05$, CI 95%) independent variables using Spearman's correlation scores are used to mine statistically significant COBs, which are then validated against CAS scores. It is important to mention here that, based on COB parameters, the *severity of anger* has been graded/classified as 'minimal', 'mild', 'moderate', and 'severe' by a team of three psychiatrists (average experience of 10 years, each), based on their professional experience, who have no clue (*i.e.*, blind) about the respective CAS scores. Finally, the COBs and the corresponding CAS-based anger grade are matched to evaluate the efficacy of COB in SA grading.

Pilot Study

A total of 415 perimenopausal women are recruited through web invitations from the company website from

October – to December 2021. Out of which 205 consists of the 'case' and the remaining is the 'control' group. Cases are those having a history of anger episodes as per the CAS but occasionally expressed. Among the cases, for the past *six months*, roughly about 36% have had angry outbursts (severe CAS), 24% have occasional but manageable anger episodes (moderate CAS), while the remaining 40% have SA, *i.e.*, they feel angry but never show up or express (moderate-to-severe CAS). The control group has a history of mild anger episodes (minimal-to-mild CAS) or nil anger. *Informed consent* has been obtained from each subject before the study. A recent (*a month-old*) laboratory data of HbA1c (to note the chances of insulin resistance, normal range $<5.7\%$), serum E2, normal range 30-400 pg/ml) [40], TSH (normal range 0.35-4.94 mIU/L) [41], and cortisol (normal range 10-20 mcg/dl when taken between 6-8 am) [42] are collected. Heart rate (normal range 60-100 bpm), Age of the subject, BMI (normal range 18.4-24.9), systolic BP (SBP, normal value is less than or equals 110-120 mmHg), diastolic BP (DBP, normal value is less than or equals to 68-80 mmHg) levels are also noted at the time of the test. Lyfas HRV biomarkers, such as SDNN (normal range 50-90 ms), RMSSD (normal range 41-60 ms), pNN50 (normal range 9-12%), SD2/SD1 (normal range 1-2), and LF/HF (normal range 1-1.8) are captured by Lyfas tests, [43] [44] [45] which are taken three times a day – 7 am, 2 pm, and 10 pm for the *same period* for examining the differences in readings at different times of a day. Anger episodes are noted daily as per the Clinical Anger Scale (CAS) [22] for the same *two weeks* period.

E. Statistics

Z-score Normalization

In this work, factor/parameter-wise *z-score normalization* is performed before conducting data analysis. Data normalization is an important pre-processing step to convert the values of the attributes within the same scale. The z-score method of normalization normalizes each value of the dataset in such a way that the mean of all values is '0' and the standard deviation is '1' [46]. The advantage of z-score normalization is that it handles outliers better compared to the max-min normalization method [47].

Step-by-Step Data Analysis

Descriptive data analysis (estimation of mean, median, max-value, min-value, and standard deviations) has been performed to note the central tendency of the original data in the sample [48][49].

Table 1 shows the results of descriptive statistics. Table 2 showcases the mean and median differences between the case and the control groups.

Kolmogorov-Smirnov tests, skewness, and kurtosis are performed to conduct the normality test, i.e., whether the data in the sample is normally distributed or not [50] (see Table 3).

The internal consistency of the data has been tested by computing *Cronbach's alpha* (α) and the computed α -value can be seen in Table 3 [51].

Mann-Whitney U test and the p-value (CI 95%; p-value <0.05) have been performed to note the median

difference between the study and control groups. The null hypothesis (the groups are the same) is rejected if the p-value is smaller than 0.05 and the score of 'U' is less than or equal to the critical value (obtained from the U table), the null hypothesis is rejected [52].

Later on, the strength of correlations (denoted by ρ) between the parameters and CAS and their statistical significance ($p < 0.05$, CI 95%,) are computed. The results can be noted in Figure 3 and Table 4. It shows how strongly COBs and other biophysical parameters are correlated to the CAS (which is a well-acclaimed gold-standard anger grading scale) with the help of *Spearman's rank correlation* [53].

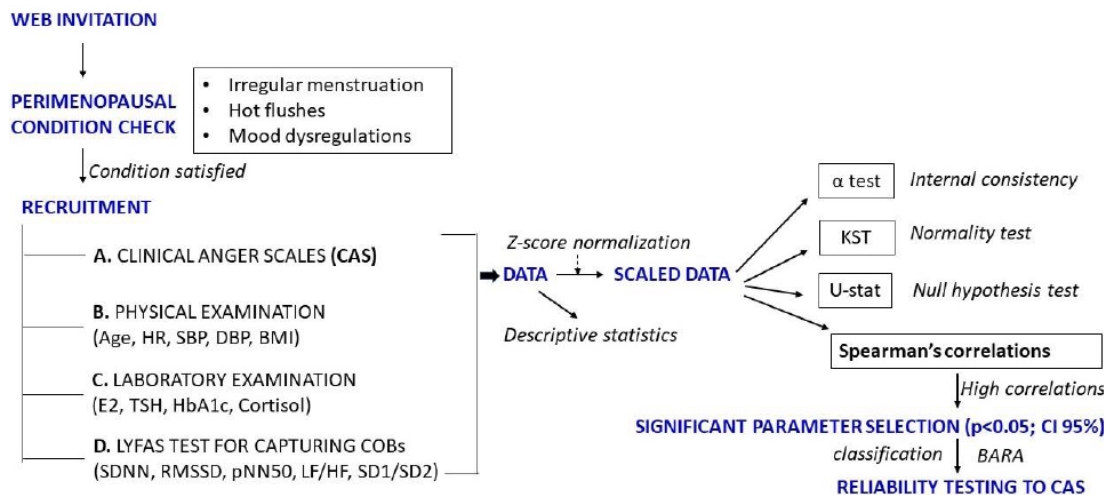


Figure 1: Flow diagram of the study.

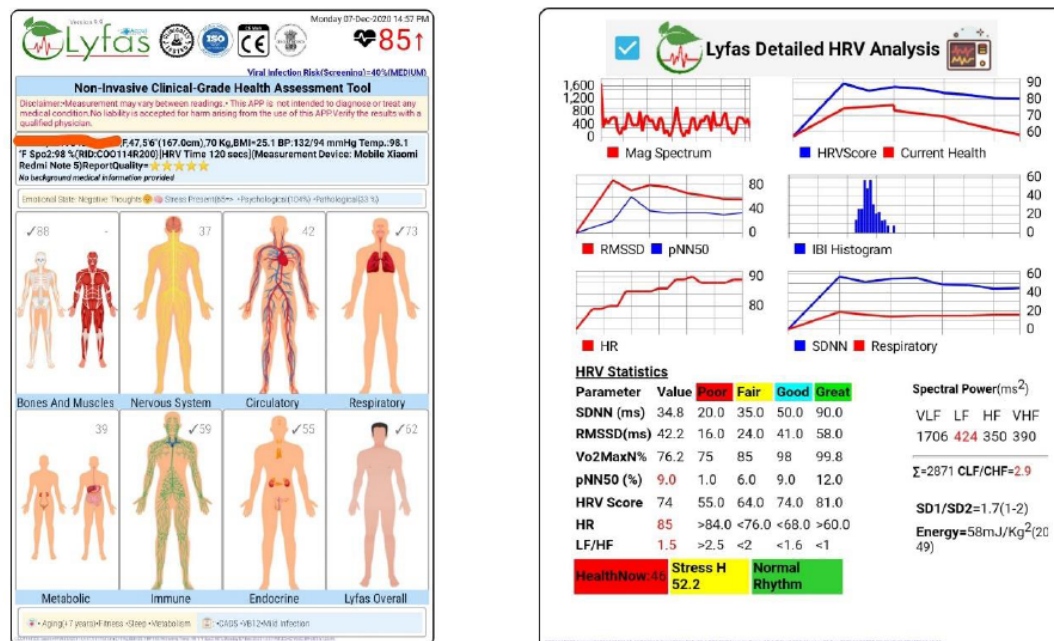


Figure 2: A sample Lyfas HRV analytics of one perimenopausal woman.

Table 1: Descriptive Statistics of all Variables in the Study Cohort

	N	mean	stdev	min	25%	50%	75%	max	Skewness	Kurtosis
Age (yr.)	415	49.21	3.65	43	46	50	52	55	-0.077	-1.182
BMI		25.42	5.20	18	21	25	29	36.8	0.340	-0.979
SBP (mmHg)		125.98	21.55	100	111	118	140	180	0.969	-0.193
DBP (mmHg)		84.74	17.89	65	72	78	93	130	1.110	0.114
HR (bpm)		82.83	11.80	65	74	80	88.5	110	0.896	-0.244
E2 (pg/ml)		213.96	103.88	30	132	209	308	400	0.009	-1.092
CORTISOL (mcg/dl)		15.03	3.15	10	12	15	18	20	0.008	-1.249
HbA1c (%)		4.91	1.90	1.01	3.68	5	6	8	-0.254	-0.695
TSH (mIU/L)		4.14	2.18	0.51	2.48	4	6	8	0.186	-0.987
SD2/SD1		1.96	0.62	0.9	1.51	1.98	2	3	0.519	-0.666
LF/HF		2.44	1.31	1.00	1.41	1.79	3	5	0.829	-0.729
SDNN (ms)		60.70	13.42	39.7	50	60	70	90	0.354	-0.732
RMSSD (ms)		63.05	14.18	40	52	61	70.15	95	0.496	-0.583
pNN50 (%)		30.68	17.33	5	19	25	38	75	1.058	0.123
CAS		21.06	19.55	1	5	10	37	63	0.763	-0.898

Afterward, the strengths of agreements (*i.e.*, the reliability) between each significant parameter and CAS scores are estimated using *Bland Altman's reliability assessment (BARA)* [54] presented in Figure 4.

Finally, the *efficacy* of the COB-based SA grading method (*i.e.*, phenotyping) with the help of Lyfas has been estimated by calculating the recall (R), specificity (SP), precision (P), accuracy (A), Youden's index or j-stat (J), and fscores (F) when compared to the CAS scores (refer to Table 5).

In this comprehensive but concise Lyfas analytics sample report of SA, it is evident that the SDNN score is close to 'poor', RMSSD is good, and the heart rate (HR) and LF/HF are high, which indicates a poor parasympathetic compensation and sympathetic overdrive, respectively. For privacy issues, the subject's information has been kept hidden.

RESULTS

This section shows the results of the experiments. Elaborations of the results are in 'discussions', which is the next section.

Table 1 shows the central tendency of the study population (a mixture of both the case and control). Parameter-wise differences (mean and median) between the case and the control groups can be seen in Table 2.

Table 2: Mean and Median Differences (Parameter-wise) between the Case and the Control Groups

Parameters	Mean		Median	
	Case	Control	Case	Control
Age	49.88	48.56	50	48
BMI	29.70	21.22	29	21
SBP	141.43	110	140	112
DBP	97	72.8	94	73
HR	89	76	89	77
E2	207	221	196	226
CORTISOL	14.82	15	14	16
HbA1c	6.3	3.49	6	3.77
TSH	5.91	2.41	6	2.51
SD2/SD1	2.39	1.53	2	1.55
LF/HF	3.49	1.4	3	1.4
SDNN	34.95	65	34.1	64
RMSSD	70.50	55	71	58
pNN50	39	22	39	23
CAS	37	5	38	5

Table 2 shows the well-comparable data of the case and the control group. Cells containing abnormal values are marked red. It is worth noting that severe CAS scores can be seen in cases with low SDNN values, high LF/HF, and SD2/SD1. RMSSD and pNN50

are found within normal limits in both groups. It is also important to note that cases are mostly obese, have high BP and HR, and have diabetic and hypothyroid traits. E2 and cortisol are found within the normal limits in case and control.

Table 3: Results of Kolmogorov-Smirnov (KST) and the Cronbach's α Test

	k-stat	p-value	α
Age	0.10023	0.00044	0.8253
BMI	0.0967	0.00078	
SBP	0.2190	5.7312	
DBP	0.2190	5.7421	
HR	0.1809	2.3092	
E2	0.0730	0.0226	
CORTISOL	0.1211	9.0472	
HbA1c	0.1014	0.0003	
TSH	0.1009	0.0003	
SD2/SD1	0.2625	9.7698	
LF/HF	0.2460	1.3197	
SDNN	0.0688	0.0373	
RMSSD	0.0876	0.0031	
pNN50	0.2096	1.7728	
CAS	0.2253	5.4069	

Mann-Whitney U-test (the independent group test) gives the U-stat value less than the critical value, while the calculated p-value is smaller than 0.05, rejecting the null hypothesis. Hence, the case and the control group have a significant median difference and are independent of each other.

In this table, except for E2 and Cortisol (grey-highlighted cells), all parameters are significant correlators (p-values < 0.05; CI 95%) of the CAS scores, as can be seen in Figure 3. The P-scores denote the strength of the correlation, expressed in decimals. The top three ranked parameters are

- RMSSD (rank-1),
- LF/HF (rank-2), and
- BMI (rank-3), which shows high positive correlations with CAS scores.

The above plots corroborate that the parameters are almost 100% reliable diagnostic biomarkers of SA as the proportional bias is close to 0.0. E2 and Cortisol are not considered in the BARA test as these are already found statistically non-significant.

Table 5: Classification Metric for Measuring the Efficiency of COBs (N=415) to CAS Scores

TP	FP	TN	FN	R	SP	P	A	F	J
297	23	82	13	0.95	0.78	0.92	0.71	0.94	0.74

Table 4: Spearman 'Significant' (p<0.05) Correlators

	p-value	P-scores	Interpretation for Anger
Age	0.0362	0.09	Age does not have a <i>strong positive correlation</i> (only 9%) but is statistically significant
BMI	5.57e-64	0.65	A statistically significant <i>strong positive correlation</i>
SD2/SD1	8.206e-71	0.61	
SBP	2.02e-52		
DBP	4.81e-50		
HbA1c	7.234e-56		
E2	>0.05	0.003	
Cortisol		0.05	
HR	2.32e-14	0.41	A statistically significant <i>strong positive correlation</i>
TSH	4.600e-63	0.62	
LF/HF	4.735e-74	0.66	
SDNN	3.133e-05	-0.23	A statistically significant <i>weak negative</i> correlation
RMSSD	3.365e-23	0.69	A statistically significant <i>strong positive correlation</i>
pNN50	3.020e-08	0.33	A statistically significant <i>weak positive</i> correlation

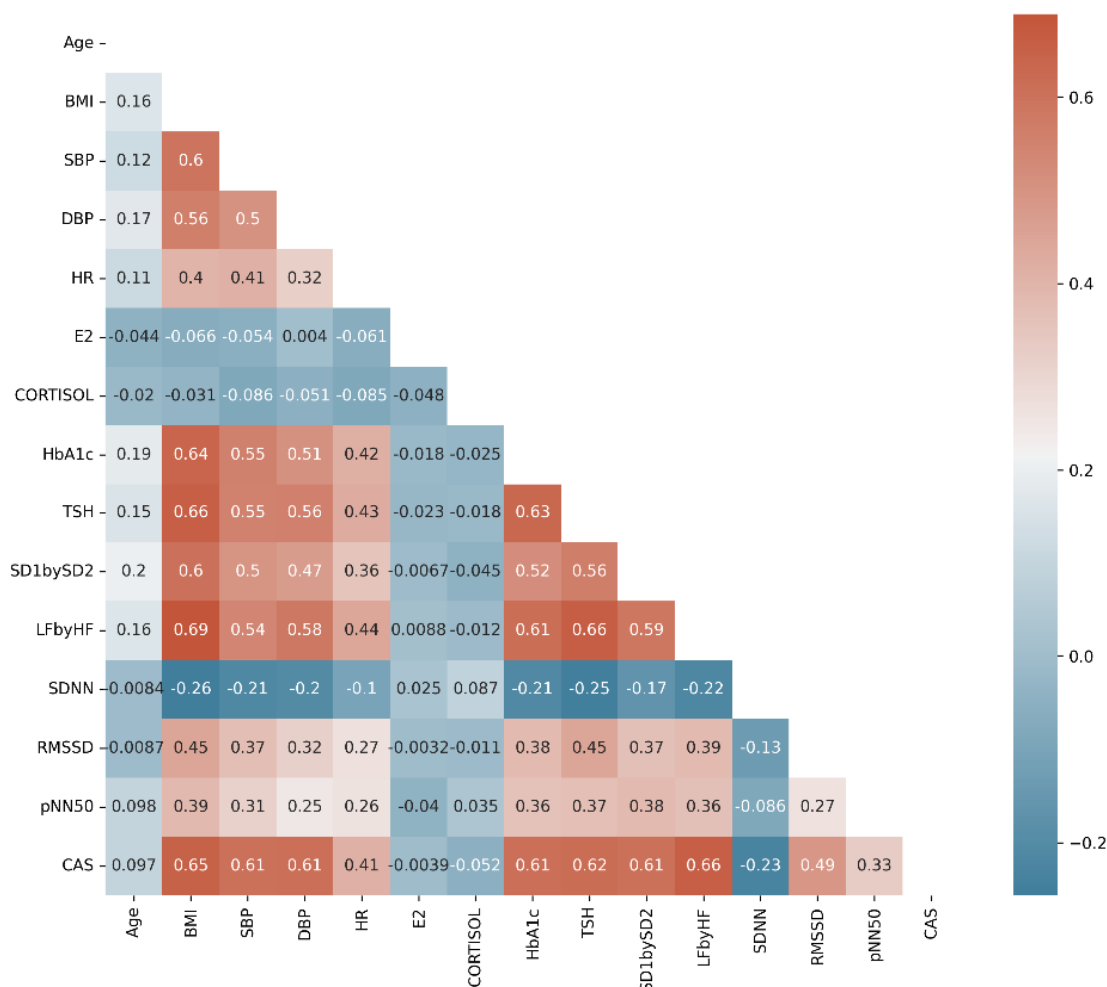


Figure 3: Spearman's correlation heatmap (P-scores).

DISCUSSIONS

Anger is a normal emotion. It is a compensatory mechanism for external and internal stress. Anger can either be expressed or suppressed. A fit of uncontrollable anger is pathological and has serious adverse cardiometabolic effects such as impulse control disorders, sudden cardiac death, violent suicide, or physical abuse. In our society, women have to walk through a hormone-regulated life. E2 and progesterone are two key hormones that control their mood and mental health. In the perimenopausal period due to the endocrinal dysregulations, they often suffer from less compensatory mechanisms to the anger bursts, which are sometimes expressive but often suppressed as evident in this study. Testosterone also plays a vital role in anger, as seen in males. A higher testosterone-E2 ratio could be responsible for anger in the perimenopausal phase of their life. Thyroid hormones play a critical role in mood control and for

many such cases, hypothyroidism is the hallmark feature.

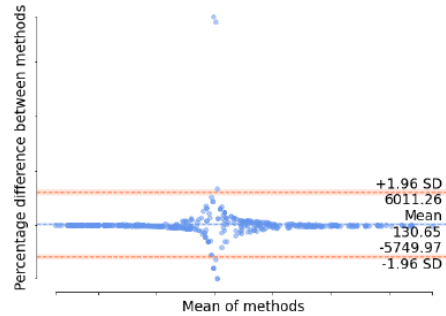
In this work, the KST-stat shows that the data is not normally distributed, as a usual finding in biological samples. Spearman's correlation (ρ) study shows that all the parameters are significantly ($p < 0.05$, CI 95%) to CAS to predict SA, except the E2 and Cortisol. In general, studies reveal that E2 and progesterone levels are raised during anger [55] so as with the Cortisol level as an adaptive response to the anger-induced threat mechanism [56]. *High positive* correlations can be seen between CAS and BMI corroborating the fact that being overweight often leads to higher episodes of mood swings, which is further supported by the study of [27]; CAS and LF/HF (high sympathetic or less parasympathetic drive) each has a ρ score of 0.65; followed by TSH ($\rho = 0.62$, high mood swing seen in hypothyroidism); HbA1c (mood disorders associated with diabetics), SBP, DBP (mood issues and irritations found with hypertensives), and SD2/SD1 (reflects heightened anxiety episodes with $\rho = 0.61$), each; while

negative correlations are found in SDNN ($\rho = -0.23$) as high SDNN reflects good mental health state, and no correlation is evident in E2, Age, and Cortisol (ρ close

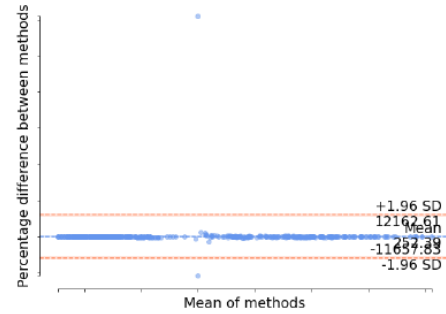
to 0).

Results of BARA show the average proportional bias close to 0.0 and a standard deviation of 1.1597,

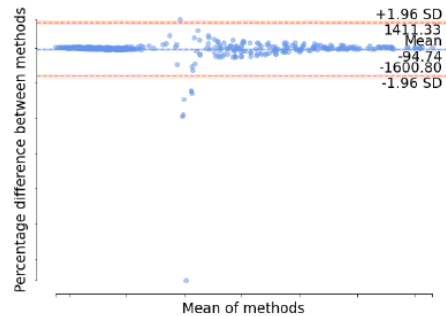
BARA test results



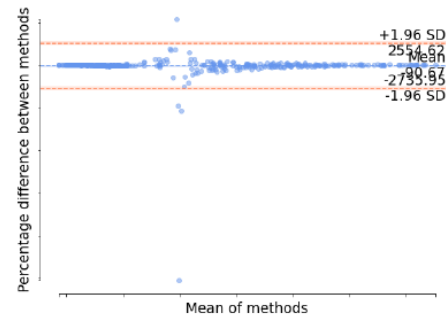
(a) Age-to-CAS



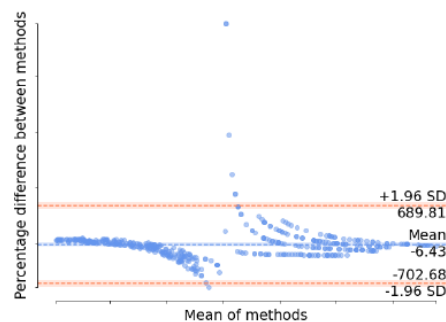
(b) BMI-to-CAS



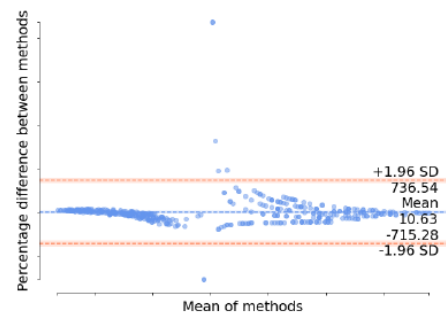
(c) SBP-to-CAS



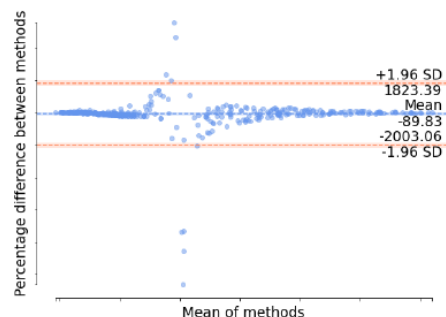
(d) DBP-to-CAS



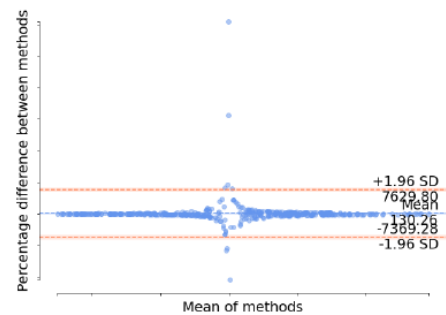
(e) HbA1c-to-CAS



(f) TSH-to-CAS



(g) HR-to-CAS



(h) SDNN-to-CAS

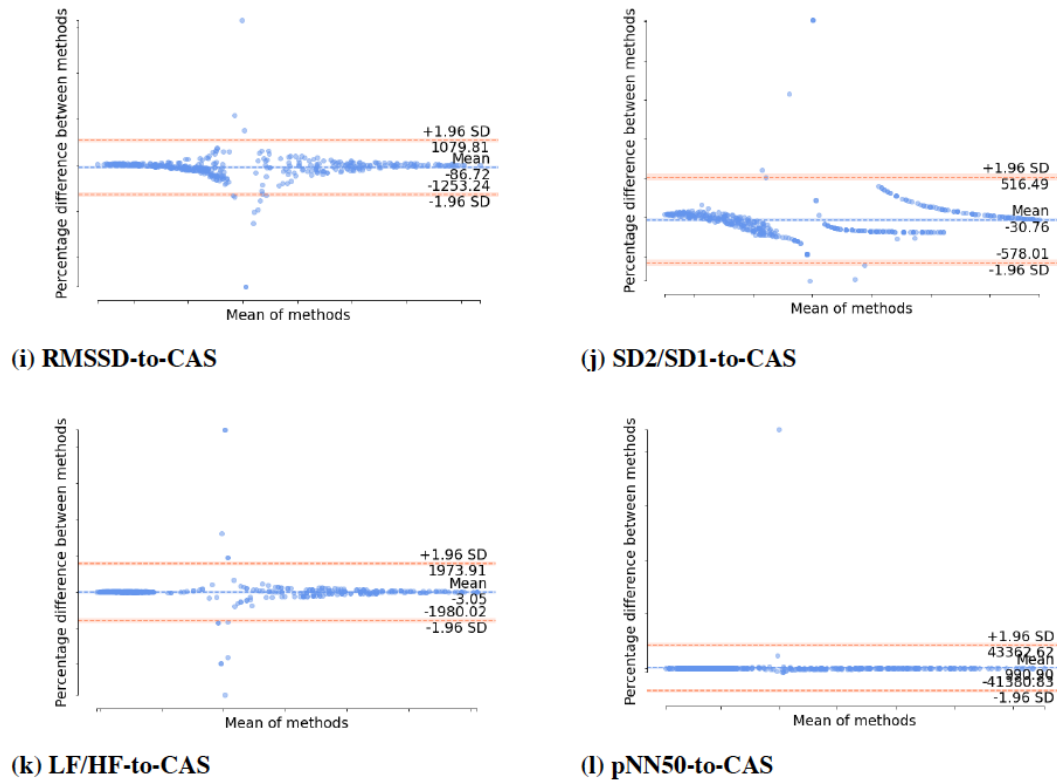


Figure 4: BARA inter-reliability plots of COBs parameters (novel instrument) to CAS.

which supports the fact that the inter-rater reliability of COBs is almost 100% when tested to CAS.

The efficiency of COBs in grading the anger episodes has been compared to the CAS. Results show that COBs have 95% recall, 78% specificity, 92% precision, 71% accuracy, 94% fscores, and 74% J-stat score, which argues in favor of using COBs as a novel hybrid and efficient instrument for anger screening and monitoring in a clinical setup.

Lyfas is a novel, pervasive, and non-invasive cutting-edge smartphone application that provides psychophysiological insights based on COBs, which surrogate for the cardiac autonomic modulation (sympathovagal balance) due to mental and metabolic dysregulations of the body. Two key COBs *i.e.*, RMSSD and LF/HF, and high BMI as one important physical parameter are directly correlated to SA. On the other hand, SDNN shows a negative correlation with anger. It is worth noting that SDNN and RMSSD surrogate for the parasympathetic compensation of the sympathetic overdrive, which occurs during anger. The authors postulate that low SDNN may play a crucial COB in the surrogate for the origin of anger. A low SDNN might be a useful COB for anger. Earlier LF/HF has been the key COB of anger, this study has added

SDNN as another important COB. RMSSD is a significant COB that surrogates for how the anger would be vented. Low RMSSD (lower parasympathetic compensation) could be a significant COB surrogate to EA, while the high RMSSD scores direct more towards SA. Figure 5. shows the COB-based anger phenotyping.

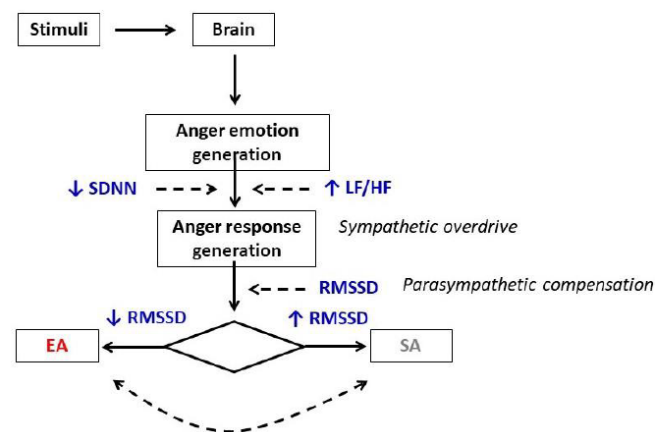


Figure 5: Lyfas COB-based anger phenotyping model.

Therefore, the *contribution* of the study lies with the successful phenotyping of SA non-invasively with the help of COBs in a much more personalized and pervasive manner with the help of Lyfas biomedical

application. SDNN and RMSSD are two new anger COBs, found in this comprehensive diagnostic reliability study.

CONCLUSIONS

The perimenopausal phase of a woman is stressful due to hormonal imbalance and associated metabolic disorders as comorbidities. Perimenopausal women who present with *high LF/HF* (known anger biomarker), *low SDNN* (new anger biomarker), *RMSSD* (new anger biomarker), and *high BMI* [56] could have SA episodes due to sympathetic overdrive. On the other hand, low SDNN and low RMSSD scores could be good COBs of EA, which are studied extensively in this paper.

To date, there is no direct instrument to measure their anger states. Questionnaire-based instruments have their limitations. Therefore, Lyfas may be a reliable (j-stat of 74%, the accuracy of 71%, and the precision of 92%), non-invasive, and pervasive clinical option for detecting the state of SA at a much early state in a personalized manner and managing it appropriately not only to pull-up the quality of life but also to prevent cardiovascular and other metabolic and mental diseases from occurring with time. This is the societal impact of the study.

ETHICAL CLEARANCE NUMBER

ECR/1181/Inst/KA/2019, dated 30-01-2020 [18]

CONFLICT OF INTEREST

The authors affirm that there is no conflict of interest at the personal or organizational level.

AUTHOR CONTRIBUTION

SC and RD conducted the study. SC conceptualized the data and analyzed it, correlated the data clinically, and wrote the paper. RD has developed the Lyfas application, reviewed the results and the analysis, and the final manuscript.

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ABBREVIATIONS

ANS, Autonomic nervous system; **APPG**, Arterial photoplethysmography; **BARA**, Bland Altman reliability

assessment; **BMI**, Body mass index; **CAM**, Cardiac autonomic modulation; **CAN**, Cardiac autonomic neuropathy; **CAS**, Clinical anger scale; **CI**, Confidence interval; **COBs**, Cardiovascular optical biomarkers; **DBP**, Diastolic blood pressure; **E2**, estradiol; **EA**, Expressed anger; **HbA1c**, Glycosylated hemoglobin; **HR**, Heart rate; **HRV**, Heart rate variability; **KST**, Kolmogorov-Smirnov test; **LF/HF**, Low by high-frequency signal wave; **MAO**, monoamine oxidase; **PCG**, Photochromatography; **pNN50**, the percentage of sinus NN intervals that differ over 50 msec; **PPG**, Photoplethysmography; **PRV**, Pulse rate variability; **PWV**, Pulse wave velocity; **RMSSD**, Root mean square of successive RR interval difference; **SA**, Suppressed anger; **SBP**, Systolic blood pressure; **SD2/SD1**, the ratio of Poincare plot of the standard deviation of the perpendicular to the line of identity; **SDNN**, Standard deviation of NN interval; **TSH**, Thyroid-stimulating hormone; **U**, Mann-Whiney U-test.

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