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A Framework for Testing the Reliability and Validity of a Novel Non-Invasive Digital Biomarker Instrument Using Statistical Techniques: A Case Study with Lyfas

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ABSTRACT

Background: This paper demonstrates a framework for testing of efficacy (reliability and validity) of a novel instrument against a gold-standard instrument. Lyfas is a novel, non-wearable, non-invasive, and economic optical biomarker instrument that runs on android smartphones. By capturing the Pulse Rate (PR) and Pulse Rate Variability (PRV) from the index finger capillary using photoplethysmography, it measures the Cardiovascular Autonomic Modulation (CvAM). The Polar H10 sensor is a gold-standard electrical biofeedback instrument that comes with a wearable chest belt and is a relatively costly device. It captures the Heart Rate (HR) and Heart Rate Variability (HRV) that surrogates Cardiac Autonomic Modulation (CAM). Objective: To showcase the statistical framework in mining the efficacy of Lyfas as a biofeedback instrument by comparing it with that of the Polar H10 instrument following a '6Minute Walk Test'. Method: Using Lyfas and Polar H10 HR sensor, PR and HR were captured from 567 subjects(n=567, 312 healthy adult males, and 255 females, respectively). The data was checked for the (a) internal consistency (Cronbach's alpha), (b) its distribution (Q-Q plots), (c) descriptive statistics (box plots), (d) Root Mean Square difference between the HR and PR, (e) reliability (Bland-Altman Reliability Test), and (f) correlations using (i) Pearson's inter-class correlations (r), and (ii) Linear regressions (R^2). Results: The *efficacy* of Lyfas as a biofeedback instrument has finally been computed by averaging the mean scores of BART (93.53%), 'r' (86.96%), and R^2 (87.58%) for the sample and found to be 87.27%. Conclusion: Lyfas can also be used as a biofeedback instrument.

Keywords: Mobile health; mHealth; Biofeedback instrument; Heart Rate; Lyfas; Polar H10 HR sensor; Bland-Altman test; Q-Q plot; Pearson's correlations; Linear regressions; 6Minutes Walk Test; Reliability test; Validity test.

INTRODUCTION

To the authors' knowledge, commercially available optical biomarker instruments have never been tested so far with an electrical biofeedback instrument to examine whether the former can serve the purpose of the latter. Biofeedback instruments are popularly used in wellness

programs and sports medicine, whereas, biomarker instrument such as Lyfas is used for evaluating the mind-body homeostasis. Moreover, no study has been reported to date on the process of examining the reliability and validity (together termed as the efficacy in this paper) of such biomarker instruments in comparison to a biofeedback instrument in any healthcare setup. Although reliability and validity are synonymous terms, yet, there is a subtle difference between the two. The reliability of an instrument refers to the degree to which the instrument yields a consistent result, while validity is the measure to the degree to which an instrument accurately measures at per to what is desired [1]. The authors propose that an *efficient* instrument is both reliable and valid. Testing the reliability and the validity of an instrument in the healthcare setup is essential.

Mobile health, popularly termed as *mHealth* is in high demand in today's digital healthcare. Key reasons behind such an increasing demand are its (i) ubiquitousness i.e., ease of accessibility from anywhere at any time, (ii) non-invasive i.e., there is no breach of skin and no need for any kind of penetration into the body while using it, and (iii) rising number of smartphone users across the world (currently it is 3.80 billion i.e., 48.16% of the population, which is 67% higher than that of the number of smartphone users in 2016) [2]. It is forecasted that by 2023, the number of smartphone users would rise to 7.33 billion and by 2025, 72% of internet users would solely use smartphones and not PCs, tablets, or laptops to access the Internet [2]. The rapid advancement of mobile technologies, instruments, software, and a continuously widening network coverage area by the telephone companies is facilitating the rapid evolution of eHealth into mHealth globally [3]. The projected market size of mHealth would be USD 156.82 billion by 2026 from 34.14 billion in 2020, i.e., a gigantic 460% growth in the business. The key reason could be the significant cost saving of healthcare delivery, especially for chronic illness management, where multiple consultations are required [3].

Cardiovascular diseases (CVD) are on the rise globally, even among sportspersons [4]. Sudden Cardiac Death (SCD) is not unusual these days [4]. According to the World Health Organization (WHO) report, Cardiovascular diseases (CVD) claim 17.9 million lives annually and are the leading cause of premature death [5]. The most common causes of CVD deaths are heart attacks, strokes, rheumatic diseases, vasculopathy, and sometimes due to various neuromuscular diseases [5]. Accessibility to healthcare is still a global challenge due to cost, physical distance, and time. Therefore mHealth technologies are into a rising adoption within the existing eHealth systems to screen, monitor, and diagnose cardiac risk in a much-personalized manner by its wireless internet technology, wider coverage, ubiquitous features, and in-built analytics [6]. However, the reliability of such a mHealth instrument needs to be assessed by validating against a gold-standard well-acknowledged instrument.

Biofeedback tests are popular to test both cardiopulmonary coherence and endurance among sportspersons, especially the Heart Rate Variability (HRV) Biofeedback tests [7]. During moderate to vigorous exercise, the heart and the lungs must work synchronously to supply the high demand of oxygen to the tissues under stress through the blood at a much higher rate. Asynchrony between the two leads to premature fatigue (as tissues are devoid of adequate oxygen) and breathlessness (lungs are run out of oxygen) or even unstable angina (heart's oxygen supply is compromised of and on) to acute myocardial infarction (death of some portions of the cardiac tissue as a result of acute oxygen deprivation). Moreover, using biofeedback, the underlying cardiopulmonary diseases are unveiled as the body is put under

exercise-induced stress [8]. Blood Pressure (BP) [9], VO_2Max [10], Heart Rate (HR) and HRV biomarkers [11], SpO_2 [12], etc. are key measures to interpret the biofeedback results.

Aim and objective of the study

i) Standardizing the process of testing the reliability and validity, i.e., the efficacy of a novel smartphone-based biomarker instrument,
ii) Testing the efficacy of Lyfas as a biofeedback instrument when compared to a gold-standard biofeedback instrument namely Polar H10 HR sensor, and
iii) Testing the usefulness of the 6-Minutes Walk Test (6MWT) in comparing the PR captured by Lyfas and HR obtained by Polar H10 sensor. This is to validate the efficacy and efficiency of the proposed efficacy technique by a rigorous experiment.

MATERIAL AND METHOD

The study protocol was approved (No. ECR/1181/Inst/K.A., 2019, dated 30th January 2020) by the external ethical committee, namely *Vagas Institutional Ethics Committee review board*. Written informed consent has been obtained from all participants before the tests as per the Helsinki norm.

- **Instruments**

Instrument 1: Lyfas is a smartphone-based wireless non-invasive biomarker instrument with a focus to assess the mind-body homeostasis in the test-takers [13] [14] [15]. It is developed by an Indian company Acculi Labs Pvt. Ltd. Bangalore [16]. Lyfas captures the *Pulse Rate (PR)* and *Pulse Rate Variability (PRV)* from the capillary circulation of the index fingers when it is placed on the mobile camera (comes with an in-built optical sensor) using the technique of arterial photoplethysmography [16]. PR and PRV surrogate for the *Heart Rate (HR)* and *Heart Rate Variability (HRV)*, although PR depends on the peripheral vascular state e.g., arterial stiffness caused by sympathetic overdrive leading to endothelial damage during stress [17]. PR measured for two minutes is considered to be the foremost physiological parameter to assess any patient clinically [18]; because it surrogates for the *Cardiovascular Autonomic Modulation (CvAM)*, [19]. Lyfas measures PR in just two minutes. Its in-built proprietary analytics assesses the mind-body state of homeostasis.

Instrument 2: Polar H10 HR sensor is a widely used gold-standard champion biofeedback instrument, used during physical exercise when worn on the chest with a belt [20]. Heart Rate Variability Biofeedback training is a method by which one controls an unusually low breathing rate to reach cardiac coherence that improves CAM [21]. It can be connected to multiple types of training instruments via Bluetooth and ANT+ [22]. The sensor comes with a soft adjustable sensor for wearing it in the chest with the sensor touching the skin of the chest to capture the HR in real-time.

Fig. 1 shows the snapshot of the application of Lyfas and Polar H10 HR sensor logger at the same time before and after the 6-Minutes Walk Test (6MWT).

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Fig. 1. Lyfas and Polar H10 HR logger applied simultaneously after 6MWT

- **The 6MWT** [23]

The 6MWT is a sub-maximal exercise test where typically a healthy adult can traverse 400 – 700 meters distance, known as 6-Min Walk Distance (6MWD) in 6 minutes with an average walking speed of 3-4 miles/hour. The key purpose of the test is to assess aerobic capacity and endurance [24]. For the present study, (i) HR and PR (measured as the beats per minute for two minutes and then the average values are considered), (ii) SpO_2 (%) is measured using a standard pulse oximeter, and (iii) BP (in mm Hg) was also measured using a BP instrument prior and after the walk.

All test takers wore the Polar H10 HR chest belt where the sensor touches the anterior chest wall and the average HR was measured twice - before and after the walk. Similarly, Lyfas tests were taken before and after the walk by touching the index finger on the rear main camera of the smartphone with the LED light 'on'. It is important to note that the HR and PR after the completion of the 6MWT were compared and not the pre-test rates, as the study aims to examine Lyfas as the plausible biofeedback instrument similar to the Polar H10 HR sensor after the exercise.

- **Study population**

In this work, the *agreement* between Lyfas PR biomarker and Polar H10 HR sensor was examined on 312 *healthy* adult males with the mean age of 35.6 years, the median age is 35 years, mean BMI is 23.44, median BMI is 23.12 and 255 healthy adult females having the mean

age is 38.8 years, the median age is 38 years, mean BMI is 23.74, the median BMI is 23.62. BP, SpO_2, PR (by Lyfas), and HR (using Polar H10) had been captured before and after the *6MWT* [25]. Table 1a and 1b give the details of the captured data. All the subjects took the 6MWT at the clinical set up of the Acculi Labs Pvt. Ltd. Bangalore India under the guidance of two in-house physicians.

- **System information**

Statistical tests have been conducted with Python 3.8 (preloaded with numpy, scipy, scikitlearn, pandas, matplotlib, pyCompare, seaborn, and statmodels), Spyder editor version 6, IPython version 7.26.0 on a Windows 10 Pro OS with Intel core processor and 8 GB RAM.

- **Statistical approach**

a) *Internal consistency check (Cronbach's α)* for examining the internal consistency of the dataset and is the most important pre-processing step to test the fidelity of the data before it goes to actual processing with a statistical technique. An inconsistent data gives a poor output and hence it is a mandatory step. The consistency score α is expressed as a value between 0 and 1, where $\alpha \geq 0.8$ is considered ideal while $\alpha \leq 0.5$ is deemed "unacceptable" [26].

b) *Basic descriptive statistical data* i.e., the mean, median, and standard deviations of the PR captured by Lyfas and the HR captured by Polar H10 can be seen in the box plots in Fig 2.

c) *Normality* of the PR data obtained by Lyfas and HR data captured by the Polar H10 sensor for males and females has been checked with the Quantile-Quantile plots or Q-Q plots, where data falling under normal distribution is a scatter plot close enough around a 45-degree line drawn from a point close to the origin of the coordinate of two quantiles – the Theoretical Quantile (x-axis) and the Sample Quantile (y-axis), which can be seen in Fig. 4. A normality check has been performed as an important step to understand the nature of the data.

d) *Root Mean Square difference (RMSd)* is the difference between the Lyfas PR and the HR measured by the Polar H10 HR sensor. It is measured by calculating the squared difference, followed by the mean squared difference, and finally, square rooting the mean squared difference. Fig. 5 shows the line plots of PR and HR and the RMSd values for both genders. It is expressed as beats per minute (bpm) difference between the PR and HR values.

e) *Bland-Altman Reliability Test (BART)* is a popular test to assess the *inter-rater reliability* or agreement of a new medical instrument compared to a gold-standard instrument [27]. It compares the mean, bias i.e., the mean of the differences, and upper and lower limits of agreement (bias ± 1.96 x standard deviation of the difference) [28]. The two limits indicate where the true mean i.e., the future measurements are likely to lie, based on which the clinical interpretation of the agreement/reliability is made. In case the values are constantly falling outside the limits, it infers as a lack of agreement or a true biological difference and not merely a sampling issue [29]. BART results can be seen in Fig. 5.

f) *Pearson's inter-class correlation coefficient* (r) between the instruments has also been assessed for *validation*. The value of 'r' ranges from -1 to +1, where -1 and +1 indicate strong negative and positive correlations, while '0' denotes non-correlations. A study has shown that 'r' value <0.5, 0.5-0.75, 0.75-0.9, and >0.9 are considered as 'poor', 'moderate', 'good', and 'excellent', respectively [30].

g) Finally, the PR values obtained from Lyfas for males and females are regressed on the HR values obtained by using Polar H10 HR sensor using *Linear regressions* (by assessing the

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correlation of determination, which is popularly known as the R^2 values) to note how much Lyfas can predict for the Polar H10 results (see Fig. 6) for further((*validation*. R^2 values close to 1.0 indicates a good fit of the independent variable onto the regressions line of the dependent variable [31].

In the end, the *efficacy* of Lyfas has been calculated as the average of the mean scores of the BART, 'r', and R^2.

RESULTS AND DISCUSSIONS

In this section, experimental results have been shown and discussed one by one:

a) *The α values* (<0.5 in both sexes before and after the 6MWT, which is still a good score as the observed inconsistency is natural between two completely different measuring systems – one is an optical biomarker instrument (Lyfas) and the other one is the electrical biofeedback instrument (Polar H10 HR sensor). Rather than going by the quantification, the authors have emphasized the qualitative 'purpose' of the 'examinee' instrument to that of the 'examiner' one. The scores can be seen in Table 1a and 1b.

b) *Descriptive statistics* can be seen in Table 1a and 1b. here, the PR is obtained by Lyfas while HR from the Polar H10 sensor. In addition to that, BP (mmHg), and SpO_2 (%) were also measured before and after the 6MWT in males and female participants, respectively.

Table 1b shows the PR, HR, BP, and SpO_2 before and after the 6MWT in Males

MALES	Before 6MWT (α = 0.48)				After 6MWT (α = 0.44)			
	HR	PR	SpO_2	BP	HR	PR	SpO_2	BP
Min	79	70	97	118/70	89	86	92	138/96
Max	94	93	99	130/86	114	113	96	146/100
Mean	82.41	80.16	99.82	122/78	92.41	88.16	93.85	144/98.25
Median	81	80	98	121/80	92	89	94	145/99
Standard deviation	1.09	2.89	0.901	5.12/6.60	1.49	4.09	1.34	3.53/1.47
Count	312							

Table 1b shows the PR, HR, BP, and SpO_2 before and after the 6MWT in Females

FEMALES	Before 6MWT (α = 0.42)				After 6MWT (α = 0.40)			
	HR	PR	SpO_2	BP	HR	PR	SpO_2	BP
Min	76	74	98	116/60	89	92	91	140/86
Max	90	93	99	130/84	114	122	94	146/100
Mean	82.11	80.16	97.92	124/79	92.40	88.18	93.05	141/88
Median	80	78	98	125/80	92	89	93	140/89
Standard deviation	1.04	2.69	0.9	5.02/6.55	1.48	3.86	1.24	3.33/1.37
Count	255							

From the box plots in Fig 2, it is evident that the basic statistics for PR and HR captured from the males and females by Lyfas and Polar H10 sensor are almost identical.

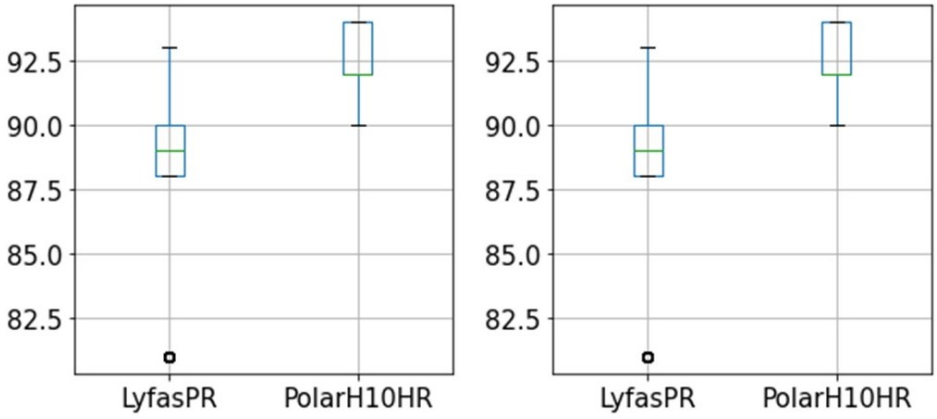


Fig. 2. Gender-wise PR (obtained from Lyfas) and HR (obtained from Polar H10 sensor) box plots and the descriptive statistics of the 6-minutes-walk test

c) *Normality test* results can be seen in Fig 3 where the Q-Q plots of PR and HR data are not normally distributed in either of the genders.

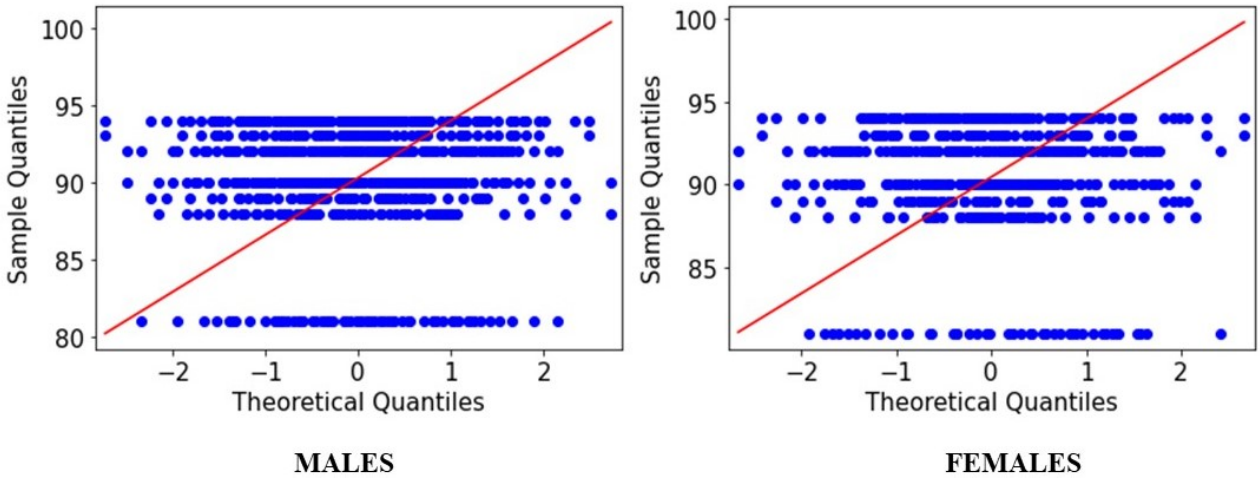


Fig. 3. The Q-Q plots

d) *Root Mean Square difference (RMSd)* between the Lyfas PR and the Polar H10 HR sensor has been expressed as bpm difference and can be seen in Fig. 4a (males) and 4b (females) line plots. It can be seen that the RMSd values between Lyfas PR and Polar H10 HR are much less for both sexes following 6MWT.

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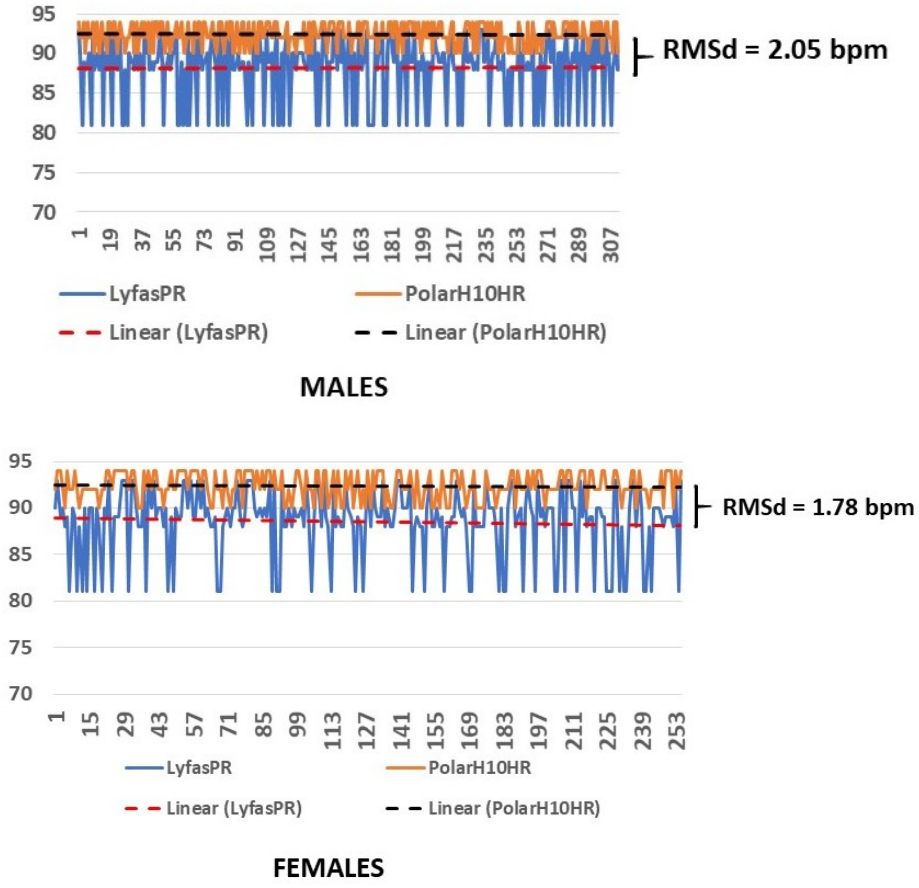
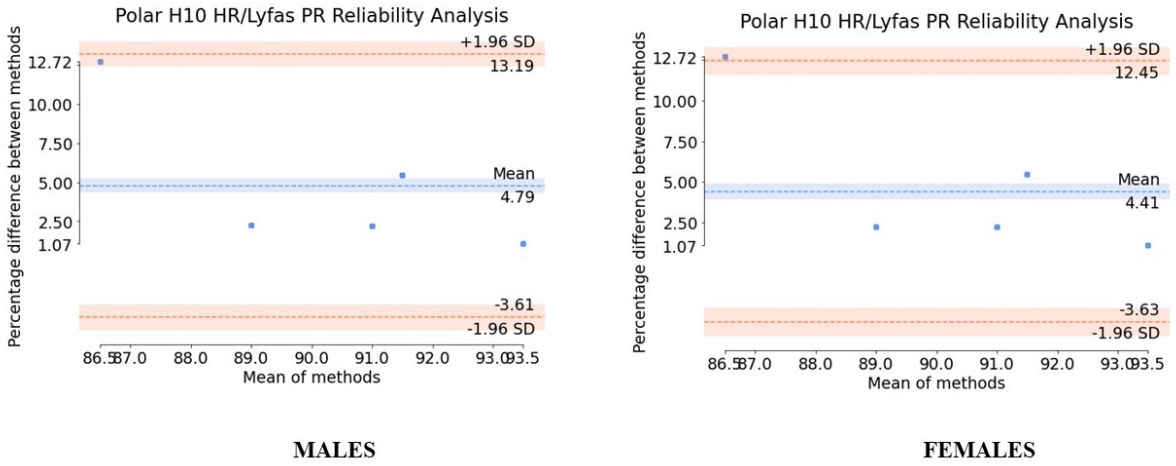


Fig. 4. Line plots of Lyfas PR and Polar H10 HR sensor and the RMSds in males and females

e) *BART reliability assessment* results can be seen in Fig. 5. The figure shows the BART plots for males and females. The light blue stripe represents the mean and mean's confidence interval., which is greater than zero in both genders. It means that the levels of retention of the Polar H10 HR and Lyfas PR are significantly different. In males, due to that 4.79 > 0 and in females 4.41 > 0 indicates that Polar H10 HR has greater retention than the Lyfas PR for both the sexes. In the plots, two pink bars represent the confidence interval at 95%, which are the limits of agreement. It states that 95% of the % difference values of Polar H10 HR and Lyfas PR for all the participants fall between 1.07 to slightly lower than 12.72 in males and 1.07 to slightly higher than 12.72 in females, which refers to the fact that there is existing 87.13 to 99.93% of agreement between the two instruments with the gross average of 93.53%. It is an encouraging result and the authors claim that Lyfas, which is a novel biofeedback instrument under examination is a reliable biofeedback instrument when compared to the Polar H10 sensor, which is the gold-standard champion instrument.

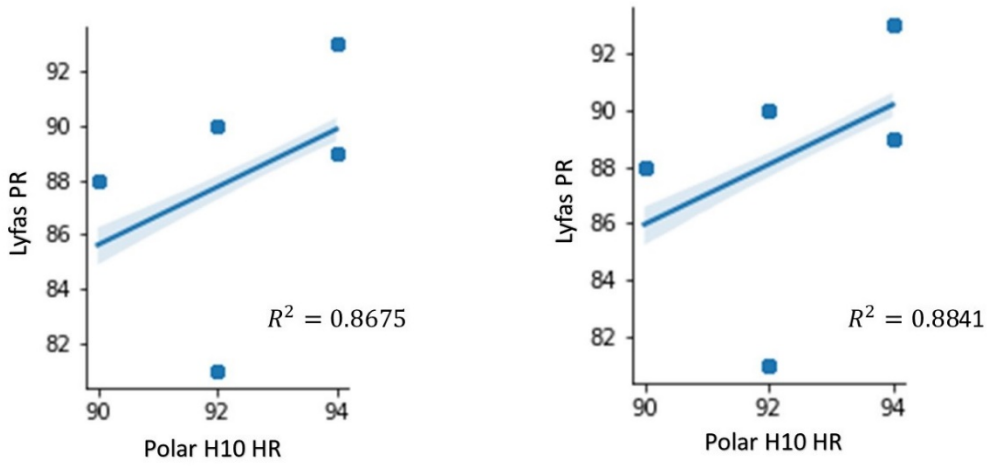


MALES **FEMALES**

Fig. 5. The BART plots

f) Further, to corroborate the findings of BART, *Pearson's correlation* (r) has been computed and found that Lyfas is 0.8616, i.e., 86.16% positive correlations for males and 0.8777, i.e., 87.77% positive correlations for females with Polar H10 HR sensor, with the gross average of 86.96%, which is 'good' as per [30] to validate Lyfas as a biofeedback instrument, quite close to the Polar H10 HR sensor.

g) Finally, the R^2 value in *linear regressions* (see Fig. 6) shows 0.8675 and 0.8841 i.e., 86.75% and 88.41% of linearity between the two instruments in males and females, respectively, with the gross .average of 87.58%. The finding revalidates Lyfas as a prospective biofeedback instrument.



MALES **FEMALES**

Fig. 6. The Regression plots

The overall *efficacy* of Lyfas is measured as the average of BART, the 'r', and R^2 values, which is 87.27% and it encourages Lyfas to be used as a biofeedback instrument. Table 2 shows the efficacy of Lyfas as a biofeedback instrument.

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Table 2. The efficacy of Lyfas as a biofeedback instrument

Statistical Test	Males	Females	Gross Average
BART	87.13 to 99.93%		93.53%
Pearson's +ve correlation	86.16%	87.77%	86.96%
Linear regressions	86.75%	88.41%	87.58%
Efficacy	***87.27%***		

Reasons for the 12.73% difference between Lyfas PR and Polar H10 HR

It is important to mention that Lyfas is a smartphone-based (runs on Android version 7 or above OS) optical biomarker instrument, work based on assessing the influence of CvAM on mind-body homeostasis using the technique of arterial photoplethysmography. It has a 30 Hz resolution, is non-invasive, non-wearable, economical, and is a ubiquitous instrument (can be used from anywhere post-installation in smartphones). On the other hand, the Polar H10 HR sensor is an electrical biofeedback instrument, based on CAM. It possesses 1000 Hz resolution, a chest-wearable sensor, and costs around INR 10000/- on purchase. PR and HR captured by Lyfas and Polar H10 HR at the 120^{th}-sec experiment show an average of 87.27% of clinical efficacy in measuring the most important vital sign of the body, i.e., the PR which refers to the HR of a person.

Therefore, the paper has showcased generically how a novel instrument can be standardized statistically to measure its efficacy in the healthcare setup, which may be replicated for examining the other biomarker instruments. Based on the efficacy study as described above, Lyfas could also be chosen as a biofeedback instrument alongside its biomarker instrument, when the Polar H10 sensor is unaffordable or unavailable. The variations, although less, between the instruments, are due to their different technical configurations, mode of use, working principles, and the state of the peripheral vasculature, and The 6MWT could be useful in assessing the reliability and validity (i.e., the efficacy) of any aspiring biofeedback instrument or otherwise.

CONCLUSION

Biofeedback instruments are popular to examine the cardiopulmonary coherence of athletes and sportspersons. They are costly and come with wearable devices that run on batteries. Smartphone-based optical biomarker instruments are gaining popularity in preventive, therapeutic, and prognostic healthcare due to their pervasiveness, being non-invasive, wireless, and economical. Authors, in this work, have proposed a statistically structured 'reliability-validity-efficacy' framework for examining a biomarker instrument that can be used as a biofeedback instrument to assess cardiopulmonary coherence in sports medicine. Such a generic framework can be used to test the efficiency of any other novel instrument that could be applied in digital healthcare.

Examining the reliability of any novel healthcare instrument is the key objective of any product to be launched in the market. To accomplish it, thorough translational research (here, a 6MWT and HR data capturing by the instruments in real-time) and quantitative data analysis using appropriate statistical methods are the important steps. The authors suggest that the framework for such extensive research should be carried out with (i) a large population size to reduce the sampling bias, (ii) simultaneous data capture by both the instruments (novel and champion, i.e., Lyfas and Polar H10 sensor, respectively), (iii) correct selection of statistical

methods in testing the data and the reliability of the novel one to the champion one, and (iv) up to date domain expertise to interpret the results. Another extensive study using HRV correlates between Lyfas optical biomarker and Polar H10 sensor has shown a high average (a) Youden's index of 80%, (b) Accuracy of 80.5%, and (c) Precision of 77.5% in the study population [32]. The study corroborates the reliability of Lyfas as an optical biomarker-based, novel, non-invasive, pervasive, economic, user-friendly (multilingual voice assisted), and reliable biofeedback instrument that runs on android smartphones.

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