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Early View

Original Research Article

Heart rate, respiratory rate and airflow variability differences between stable and exacerbating chronic obstructive pulmonary disease patients

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Heart rate, respiratory rate and airflow variability differences between stable and exacerbating chronic obstructive pulmonary disease patients.

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Author contributions

ERV and SM developed the original methodology for the study together. AJS recruited participants, collected data, analysed data and performed the linear and non-linear analysis with AM. OD helped with trial and device management. AJS wrote the initial draft of the paper AS helped with data collection and data analysis. RP created software to facilitate extraction of the datapoints in a format that facilitate subsequent processing. AJS, SM, AM, JRH made substantial contributions to the interpretation of the data. All authors reviewed and revised the manuscript critically for important

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JRH has received grant support, and payment for educational and advisory work, personally and to his institution, from pharmaceutical companies that make medicines to treat COPD.

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Take home message

Physiological variability measures significantly differ between stable and exacerbating groups of chronic obstructive pulmonary disease. This can be used to build exacerbation detection algorithms in the future leading to improved patient outcomes.

ABSTRACT

Rationale:

Earlier identification and treatment of chronic obstructive pulmonary disease exacerbations leads to improved clinical outcomes. Wearable technology has the ability to measure physiological signal variability which is likely to be different in states of stability and exacerbation.

Objectives

To analyse signals including heart rate, respiratory rate and airflow, from a novel small wearable device, AcuPebble RE100 and compare differences in a group of stable and exacerbating participants.

Methods:

Groups of stable and exacerbating adult participants with chronic obstructive pulmonary disease were asked to wear AcuPebble RE100, which records physiological signals including heart rate, respiratory rate and airflow. Linear and non-linear variability analysis was conducted on each of these time-series to detect differences between groups.

Results

A total of 51 participants (33 stable and 18 exacerbating) were analysed. Stable participants used the device for a median (IQR) of 18 nights (10 – 26). The exacerbating participants had significantly higher heart rate variability measures and a significantly lower heart rate complexity measure compared to stable participants. Respiratory rate variability and complexity were significantly increased in the exacerbating participants. Detrended fluctuation analysis demonstrated two-cross over points in both populations, with the exacerbating participants demonstrating a significantly lower median α3 (0.50 (0.47 – 0.56) vs. 0.69 (0.65 – 0.79), $p < 0.001$) compared to the stable population.

Conclusion

We have shown that significant differences exist in heart rate, respiratory rate and airflow variability measures between stable and exacerbating groups of chronic

obstructive pulmonary disease. This will help build exacerbation detection algorithms in the future.

INTRODUCTION

Earlier identification and treatment of chronic obstructive pulmonary disease (COPD) exacerbations are likely to lead to improved patient morbidity and mortality whist resulting in cost savings due to reduced healthcare utilisation and absenteeism. (1, 2) Changes in physiological signals such as heart rate and oxygen saturation have shown promise in this area, but simple linear analysis of these static signals has had limited clinical utility and failed to show a difference compared to symptom monitoring alone. (3, 4)

Wearable technology has the potential to objectively measure continuous physiological signals which are likely to change from stable to exacerbating phases and highlight earlier, potentially subtle changes prior to symptom changes. A recent systematic review looking at the role of wearables to detect COPD exacerbations, found two prior studies that have shown a high positive predictive value (above 90%) in detecting an exacerbation. However, due to high attrition rates, one of these studies only included 13 participants in their analysis, (5) and the other used a composite score relying on several parameters including environmental sensors which are costly and difficult to replicate in real world settings. (6) Moreover, continuous measurement of physiological signals generates many datapoints, meaning novel analysis methods are needed to better understand this data. Prior work looking at oxygen saturation signal variability in a small number of COPD patients has shown promise in this area, but further work in this field is necessary. (7)

The first step in creating an accurate system to detect physiological changes suggesting the start of an exacerbation, is to use a simple device that measures common physiological signals and identifies key differences between the stable and exacerbating phases of COPD. Therefore, the main objective of our work as to analyse signals including heart rate (HR), respiratory rate (RR) and airflow, from a novel small wearable device, AcuPebble RE100 and compare differences in a group of stable and exacerbating participants. This objective is important as it guides the identification of exacerbation event signatures using a simple device, which is crucial for the development of future patient monitoring systems aimed at early detection.

METHODS

This prospective cross-sectional study received ethical approval from the Health Research Authority in England (IRAS 247489; REC reference 19/NI/0194). The study was also prospectively registered with clinicaltrials.gov (NCT04495062)

Inclusion/exclusion criteria

Adult participants with a diagnosis of COPD, made with an exposure history of more than a 10-pack year smoking history and spirometry showing a post-bronchodilator forced expiratory volume to vital capacity ratio of less than 0.7 were included in the study. Participants were excluded if they were not fluent in English, had an allergy to the wearable adhesive dressing, had an impairment meaning they would not manage to use the technology on their own, had an implantable device, had a known diagnosis of concurrent sleep disordered breathing or needed ventilatory support. Participants were split into two groups: stable COPD participants, recruited from outpatient clinics with no increase in their usual respiratory symptom burden at the time of consent; and exacerbating COPD participants recruited from their hospital admission. COPD exacerbations were defined as per the GOLD guidelines, (an increase in breathless and/or cough and sputum production that has worsened in less than 14 days). (8) We only included exacerbations that led to a hospital admission, defined as severe by the GOLD guidelines. We also included only participants that were admitted specifically for a COPD exacerbation.

Wearable device

The wearable device used for this study was AcuPebble RE100. Under the scope of this study, AcuPebble was not used as a medical device, but as an acoustic monitor to acquire signals, for which it is CE marked. AcuPebble RE100 is a small circular device with a diameter of 2.9cm which attaches to the neck via a disposable medical grade adhesive. It records physiological acoustic signals and algorithms convert these sounds into respiratory rate (breath per minute (bpm)) recorded every two seconds, heart rate (beats per minute (bpm)) recorded every two seconds and airflow (normalised volt) recorded every 0.1 seconds.

Study protocol

Following informed consent, baseline data including demographics, smoking history, spirometry results, past medical, social and drug history was collected for both groups. Participants also completed two validated questionnaires: the modified Medical Research Council (mMRC) breathlessness score (9) and the COPD airway assessment tool (CAAT). (10) Participants were shown how to use the AcuPebble RE100 which connected via Bluetooth to a mobile phone. The stable COPD group were asked to use AcuPebble RE100 whilst they slept at night for up to 30 days; whilst the exacerbating group were given the device within 48 hours of admission to hospital, and asked to wear the device continuously until discharge, and following discharge nocturnally for up to 28 days. For the main analysis we compared readings between stable COPD participants and hospitalised exacerbating participants, with data capture in the first 48 hours of their admission.

Analysis methodology

When comparing readings between patients, a fixed time-series duration was necessary to avoid bias. A six-hour nocturnal time window was used for both exacerbating and stable patients (supplementary material). The average across all nocturnal stable COPD recordings was used to compare with the average initial nocturnal recordings (within 48 hours of admission) from the exacerbating group. We also looked at the nocturnal recordings five days post discharge for the exacerbating group. Recordings shorter than six hours duration were not included in the final analysis. Data recordings that had ≥ 15% of missing data in any of the time series were also not included in the final analysis.

For analysis of the heart rate (HR) and respiratory rate (RR) time series, linear and non-linear analysis methods were used. Linear measurements included the mean HR and mean RR as well as SDNN (the standard deviation of the inter-beat interval of successive heart beats (ms)), cSDNN (the SDNN corrected for mean HR), and SDBB (the standard deviation of the breath-to-breath interval (ms)).

Non-linear measurements included Poincare plot indices (SD1 and SD2) and sample entropy (SE). SD1 is a measure of short-term variability and for heart rate usually reflects the effect of respiratory on the cardiac cycle, whereas SD2 is a measure of longer-term variability. (11, 12) Sample entropy is a measure of the amount of information in a physiological signal, reflecting the engagement of physiological

control. Higher sample entropy measures indicate a more engaged system with increased information processing and increased complexity. (13) Multi-scale entropy (MSE) of both the HR and RR were also computed. MSE is an extension of sample entropy while 'zooming out' and is representative of information processing at lower resolution. (14)

Given the high resolution of airflow data available, detrended fluctuation analysis (DFA) was used. DFA is an analytic method that provides useful information on the relationship between different segments of a physiological time-series at different scales of a recorded signal. (15, 16) Preliminary analysis showed the DFA curve had two cross-over points, and this meant there was a short-term, intermediate term and long-term scaling exponent, α1, α2 and α3 respectively

All the analysis was computed using well known methods previously described in the literature, using freely available coding algorithms in MATLAB processing software. For SE calculations, settings of m at 2 and r at 0.2 were used, and MSE was calculated over ten scales.

A summary of the calculated measures can be found in Table 1. Further information can also be found in the supplementary material.

For the stable COPD population, we assessed correlations between the time series measures (Table 1) and FEV1, CAAT score and mMRC. For the exacerbating population we assessed correlations between the time series measures (Table 1) and the admission National Early Warning Score 2 (NEWS2), (17) the c-reactive protein and the Rome COPD exacerbation severity classification. (1)

We assessed usability and acceptability of AcuPebble RE100 via a standardised feedback questionnaire.

To give some context we have also included data from a historical non-COPD group in the results section. The methodology for this historical group can be found in the Supplement.

Statistical analysis

All statistical analysis was conducted using the software Statistical Package for the Social Sciences (SPSS version 29). Baseline demographics between groups was

compared using Chi squared tests for ordinal and categorical data. Continuous data were checked for normality and analysed using the independent t-test for parametric data or the Mann-Whitney U test for non-parametric data. MSE analysis at varying scales was compared using a two-way ANOVA. A p-value of ≤ 0.05 was considered to be statistically significant.

RESULTS

200 participants were screened, of which 114 met eligibility criteria, and 59 were consented for the study, 36 with stable COPD and 23 undergoing an exacerbation. Due to short recordings and subsequent ineligibility, a total of 33 stable COPD participants and 18 exacerbating participants were analysed (51 in total). The study flow diagram is illustrated in Figure 1. There were no significant differences in participant demographics between groups (Table 2) except that the participants undergoing an exacerbation had a significantly lower median (IQR) body mass index compared to the stable population, (18.9 $kg.m^2$ (17.7 – 24.5) vs. 27.1 $kg.m^2$ (21.0 – 31.8), p = 0.002). The exacerbating population had significantly more severe COPD with worse historic lung function and an increased CAAT score at the time of recruitment (Table 3).

Stable COPD participants used the device for a median (IQR) of 18 nights (10 – 26) and for a median (IQR) of 8.3 hours (6.8 – 9.8) per night. Therefore, overall, there was a total of 338/519 (65%) nocturnal HR recordings, 492/519 (95%) RR recordings and 345/519 (66%) airflow recordings available from 33 stable COPD participants.

Exacerbating COPD participants' first valid nocturnal recording within 48 hours of admission was used to compare to the stable COPD population. Following deletion of missing time-series data, 9/18 (505) HR recordings, 18/18 (100%) RR recordings and 12/18 (67%) airflow recordings were available.

Stable vs. exacerbating participants

The mean HR and RR were numerically higher in the exacerbating participants compared to the stable participants. For the heart rate time series, the exacerbating population had significantly higher variability measures with a median cSDNN (268ms (207 – 315) vs 179ms (162 – 246), p = 0.006), median SD1HR (12ms (8 – 15) vs 8ms (7 – 10), p = 0.04), median SD2HR (90ms (79 – 130) vs. 75ms (67 – 96), p = 0.037), but had a significantly lower complexity measure with a median SE HR (0.1258

(0.1044 – 0.1568) vs. 0.1607 (0.1355 – 0.1981), p = 0.015) compared to the stable population. (Table 4)

For the respiratory rate time-series, the exacerbating population had a significantly higher variability and complexity measures with a median SDBB (629ms (515 – 1126) vs. 525ms (398 – 665) p = 0.024), median SD1RR (134ms (96 – 169) vs. 92ms (76 – 109ms), p = 0.037) and median SD2RR (876ms (722 – 1584) vs. 767ms (558 – 936), p = 0.025) compared to the stable population. (Table 3)

For the airflow time-series, both populations demonstrated two cross-over points in the detrended fluctuation analysis which were at similar time points leading to three scaling exponents. (Figure S1) The exacerbating population had a significantly lower median alpha 1 (1.63 (1.61 – 1.65) vs. 1.66 (1.63 – 1.67), p = 0.005) and median alpha 3 (0.50 (0.47 – 0.56) vs. 0.69 (0.65 – 0.79), p <0.001) compared to the stable population. (Table 3)

Multiscale entropy (MSE) analysis of both HR and RR showed that the sample entropy significantly increased as the scale increased for both the stable and exacerbating groups. A two-way ANOVA test showed a significant reduction in HR MSE [F_{group} (1,20) = 17.895, p<0.001, F_{scale}(9,20) = 38.37, p<0.001]] in the exacerbating group compared to the stable group, irrespective of scale. While there was a significant increase in the RR MSE [F_{group} (1,20) = 40.703, p<0.001, F_{scale}(9,20) = 51.434, p<0.001]] in the exacerbating group compared to the stable group. (Figures 2 and 3)

For the stable COPD group, there were no significant correlations between FEV1, CAAT score, mMRC score and any of the time-series variability measures. In the exacerbating group, there was no significant correlations found between any of the time-series variability measures and the admission National Early Warning Score 2 (NEWS2), the c-reactive protein or the Rome COPD exacerbation severity classification.

Exacerbating participants: admission vs. post-discharge

For the exacerbating group, nocturnal data five days post discharge data was available in 9/18 (50%) of participants. Given small numbers, statistical analysis with Friedman's test was not computed. At five days post discharge, the mean HR was largely unchanged, but the variability measures (cSDNN, SD1HR and SD2HR) trended

downwards, while sample entropy of HR increased. While the mean RR was also largely unchanged, the other variability measures all decreased at five days post discharge compared to admission values. This is illustrated in Figures S4 and S5 (supplementary material). Airflow measures alpha 1 and alpha 2 decreased from admission to post discharge, while alpha 3 increased. This is illustrated in Figure S6 (supplementary material).

For HR, multiscale entropy increased five days post discharge at all scales (Figure S7). For RR, multiscale entropy decreased five days post discharge at all scales (Figure S8).

Usability of AcuPebble in the stable COPD population was obtained from 24/33 (73%) of participants with the majority (16/24) finding attaching the sensor very easy. Most participants (17/24) found the sensor comfortable to wear and in 20/24 the sensor stayed in place for the duration of the night. Usability feedback was obtained from 8/18 participants in the exacerbating group. All participants found the sensor at least moderately easy to put on with 75% finding it comfortable. Only one participant developed a rash around the site of the device, however, this disappeared through the day.

The results from our historical non-COPD group, using a similar device can be seen in the supplement (pp 16-20). The non-COPD group were younger and less comorbid. No significant differences were found in the heart rate and respiratory rate variability measures between the non-COPD group and stable COPD group. There was a significant difference in airflow variability measures with alpha 2 being significant lower in the non-COPD group vs. stable COPD participants (0.2367 (0.2070 – 0.2661) vs. 0.2805 (0.2600 – 0.3077), $p<0.05$). HR multiscale entropy was higher in the non-COPD group compared to the stable and exacerbating COPD groups whilst RR multiscale entropy was lower in the non-COPD groups compared to both COPD groups.

DISCUSSION

This prospective observational study has shown that significant differences exist in HR and RR variability measures between stable COPD participants and those undergoing an exacerbation. The differences are summarised in Figure 4.

Heart rate variability (HRV), measured by cSDNN, SD1 and SD2, was significantly increased in participants undergoing an exacerbation compared to the stable population. These findings are similar to previously published data by Kabbach et al (2017), who used 10-minute daytime recordings comparing COPD exacerbators to stable participants. They also found increased HR variability measures (increased SDNN, SD1 and SD2) in the exacerbating group. (18) Another study also found similar results using spectral analyses, assessing the HR variability using frequency domains, showing increased variability in the exacerbating population. (19) We did not find a statistically significant increase in mean HR in the exacerbating participants, which was 3bpm higher compared to the stable population. Previous work has suggested that day time HR typically rises by about 7bpm at exacerbation. (20) The nocturnal measurements used in this study show a smaller change.

Heart rate is controlled by the autonomous nervous system (ANS) with a complex interplay between the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). The PNS primarily impacts beat-to-beat variability, (21) and this is reflected in short term measures of HRV like SD1 HR. We found that SD1HR significantly increased in the exacerbating population, suggestive of increased short-term variability. This is likely to be due to increased respiratory sinus arrhythmia and possibly increased PNS activation. In humans, airway tone is thought to be mainly vagally controlled (22) and during an exacerbation, the increased bronchoconstriction, airway narrowing and increased vagal activity in the airway, may translate into increased PNS activity. (18)

Global ANS activity is reflected in longer term measures of HRV like cSDNN and SD2 HR. (21) We found that these longer-term measures were significantly higher in the exacerbating group vs. stable group, (cSDNN 268ms (207 – 315) vs 179ms (162 – 246), $p = 0.006$) suggestive of increased ANS activation, which is likely to be due to both increased PNS activity as described above, but probable also increased SNS activity due to the use of beta-agonists and infective / inflammatory elements that play a role in the exacerbation.

It is important to note, that while in health a higher HR variability is linked to better prognosis, this is unlikely to be the case in this situation, as increased variability relates to a stretched and heightened ANS and worse outcomes. (18)

Sample entropy quantifies the degree of irregularity vs. regularity in a time-series and measures complexity and structural richness of the signal. Low values, suggest decreased complexity, more regularity and less system engagement. It takes into account the multiple regulatory systems affecting a particular time-series. (23-25). SE HR is significantly lower in participants undergoing an exacerbation, suggesting increased regularity and less complexity. Multi-scale entropy further defines the richness / complexity of the time-series by considering the multiple timescales that exist in physiological systems. MSE analysis of HR for both groups increased, confirming that HR is a complex time-series. (26, 27) (14) Participants with an exacerbation had decreased MSE HR at all time-scales. Prior work has shown lower sample entropy of HR in septic patients, (28) cirrhotic patients (12) and that HR MSE is an independent predictor of death in patients hospitalised for trauma. (29) A reduction in entropy describes a reduction in system coupling, a less engaged system and one that cannot adapt to added stressors. (30, 31)

Respiratory rate can be affected by a myriad of different signalling pathways and a voluntary component differs in the awake and sleep state. Our work is novel, with no prior study investigating RR variability in participants undergoing a COPD exacerbation. The mean RR rose in the exacerbating population by a similar level compared to previous work. (20)

RR variability measures (SDBB, SD1RR, SD2RR) were significantly higher in participants having an exacerbation. MSE analysis of RR showed that sample entropy was also significantly higher in the exacerbating group compared to stable participants. Furthermore, the difference was more apparent at higher scales, suggesting that the increased signal complexity was more apparent when longer-term timescales were considered. This is useful in clinical practice as it suggests that wearables with a lower resolution (e.g., one sample every 10 or 20 seconds) can still provide valuable information. This increased variability and complexity can be explained in a few ways. Participants undergoing an exacerbation are more hypoxic, leading to metabolic imbalances and increased respiratory rate, coupling and engagement. During a COPD exacerbation there is greater skeletal muscle dysfunction (32) and increased hyperinflation, (33) meaning reduced efficacy of both the inspiratory muscles and diaphragm. This leads to a fall in minute ventilation, and increased engagement from the respiratory system with increased complexity.

No prior study has looked at nocturnal airflow in this population. We have shown that COPD participants have two cross-over points in DFA analysis and three exponents (α1, α2 and α3). This indicates the scaling exponent (alpha) differs for different range of scales. While there was no clinically relevant difference in α1 and α2, at longer scales (above 30 seconds), exacerbators had a significantly lower α3 value compared to stable participants (median (IQR) 0.5000 (0.4676 – 05578) vs. 0.6931 (0.6509 – 0.7931), $p<0.001$). This suggests that while stable COPD participants demonstrate long-range power law dynamics and positive autocorrelation at longer scales (whereby higher airflow is followed by higher airflow and vice versa), the exacerbating population have an α3 of 0.5, which is suggestive of white noise and completely random fluctuation. This is likely explained by increased upper and lower airway inflammation as well as bronchoconstriction, oedema and increased mucous production. This can lead to expiratory flow limitation, narrow airway calibre and increased turbulence of flow. (33)

Of note, for all the physiological time-series, there was a trend towards 'normality' or stable COPD participant values in the exacerbating participants by day five post discharge. This is important as it suggests that in the recovery phase of COPD, the variability measures return to baseline.

There are strengths and limitations to consider to this work. Participants were representative of a moderate – severe COPD population and were symptomatic, with most participants already on triple inhaled therapy. There were no significant differences in age, gender, smoking history and medical comorbidities between the groups. The exacerbation cohort had significantly worse historic lung function with a reduced FEV1, FVC and TLCO and a higher CAAT symptom score on admission. While we used the median nocturnal time as the start point of our analysis for the exacerbating population, no sleep diaries were given to patients. Therefore, we may have captured some data while COPD exacerbators were awake. This could lead to some bias, as there is evidence to suggest HR and RR variability differs during sleep compared to wakefulness. Second there was a degree of artefact in the HR and airflow recordings, meaning a small sample size and therefore a high type 2 (beta) error. Third, the patients admitted to hospital may have started their actual exacerbation at different times. In future studies, a retrospective symptom diary would be useful to pinpoint the exact start of their symptom onset. Fourth, data capture both preceding

the exacerbation and post exacerbation would have been useful to map the exacerbation trajectory. Fifth, both BMI and lung function can potentially influence the autonomic tone, thus impacting variability analysis. However, given the small numbers, multivariable analysis could not be performed. Moreover, from the stable group, no correlations were seen between any of the time-series parameters and FEV1. This suggests that differences in lung function between stable and exacerbating states are unlikely to have contributed to the differences seen.

Overall, we have shown that continuous measurements of HR, RR and airflow through wearable technology is feasible, and acceptable to patients during states of stability and exacerbation. There are clear differences in time-series variability and complexity measurements between the stable and exacerbating COPD populations (Figure 4). Therefore, understanding and integrating variability measures into clinical practice is important to be able to build exacerbation detection algorithms in the future. Future work needs to focus on identifying the point(s) at which variability measures change in a patients' exacerbation journey and whether this can be picked up objectively prior to symptoms. This will help build algorithms in the future such that treatment can be started earlier and thus avoid severe sequalae. Signal changes will also be useful for monitoring recovery and identifying those at risk of recurrent exacerbation and re-admission.

The role of continuous physiological measurement, whilst in its infancy, has great potential to change the detection and management of exacerbations, leading to improved patient outcomes in the future.

Table 1

Measure	Definition
Heart rate measures	
Mean heart rate (mean HR) (bpm)	The average heart rate
SDNN (ms)	The standard deviation of the inter-beat interval of successive heart beats
cSDNN (ms)	The SDNN corrected for the mean HR
SD1 HR (ms)	A measure of short-term HR variability
SD2 HR (ms)	A measure of longer-term HR variability
SE HR	A measure of signal HR complexity and richness
MSE HR	Multi-scale entropy analysis of HR. This looks at signal complexity when the data is 'zoomed out' at different scales
Respiratory rate measures	
Mean respiratory rate (mean RR) bpm	The average respiratory rate
SDBB (ms)	The standard deviation of the inter-breath interval of successive breaths
SD1 RR	A measure of short-term RR variability
SD2 RR	A measure of longer-term RR variability
SE RR	A measure of RR signal complexity and richness
MSE RR	Multi-scale entropy analysis of RR. This looks at signal complexity when the data is 'zoomed out' at different scales
Detrended Fluctuation analysis measures	
Alpha 1	Short term scaling exponent (roughly 3 seconds)
Alpha 2	Medium term scaling exponent (roughly 30 seconds)
Alpha 3	Longer term scaling exponent (more than 30 seconds)

Table 2: Baseline characteristics of stable vs. exacerbating participants

Baseline characteristic	Stable COPD (n = 33)	Exacerbating COPD (n = 18)	p value*
Male (%)	20 (61)	10 (56)	0.73
Female (%)	13 (39)	8 (44)	0.73
Age (years) (mean ± SD)	67 ± 10	64 ± 9	0.46
Body Mass Index ($kg.m^2$) (median (IQR))	27.1 (21.0 – 31.8)	18.9 (17.7 – 24.5)	**0.002**
Current smoker (%)	6 (18)	7 (39)	0.11
Ex-smoker (%)	27 (82)	11 (61)	0.11
Pack year history (median (IQR))	47 (25 – 64)	43 (40 – 50)	0.97
Mobility (%) • Independent • Uses a stick • Uses a frame	 • 20 (61) • 11 (33) • 2 (6)	 • 13 (72) • 4 (22) • 1 (6)	0.69
Independent with regards to activities of daily living (%)	31 (94)	18 (100)	0.29
Medical Comorbidities (%)			
Alpha-1 Antitrypsin	4 (12)	0	0.12
Atrial fibrillation	3 (9)	0	0.19
Cerebrovascular disease	0	0	-
Hypercholesterolaemia	9 (27)	5 (28)	0.97
Hypertension	11 (33)	5 (28)	0.68
Ischaemic heart disease	5 (15)	2 (11)	0.69
Oxygen therapy	2 (6)	1 (6)	0.94
Peripheral vascular disease	1 (3)	0	0.46
Type 2 diabetes mellitus	5 (15)	1 (6)	0.31

Table 3: Pulmonary function tests, baseline symptom severity assessment scores and relevant medication of stable vs. exacerbating participants

Characteristic	Stable group	Exacerbating group	p value
Pulmonary function tests* (mean ± SD)			
FEV1 (L)	1.35 ± 0.64	0.91 ± 3.22	**0.008**
FEV1 %predicted	48.96 ± 20.00	32.31 ± 10.14	**0.002**
FVC (L)	3.27 ± 1.06	2.42 ± 0.68	**0.004**
FVC %predicted	91.31 ± 25.67	70.00 ± 19.97	**0.005**
FEV1/FVC ratio	0.41 ± 0.12	0.38 ± 0.11	0.47
TLCO (mmol/min/kPa)	4.11 ± 2.34	2.46 ± 0.63	**0.023**
TLCO %predicted	48.60 ± 22.82	33.21 ± 10.78	**0.029**
KCO (mmol/min/kPa)	0.86 ± 0.35	0.65 ± 0.18	0.06
KCO %predicted	61.88 ± 25.52	48.72 ± 16.02	0.10
Symptom assessment questionnaires (median (IQR))			
mMRC breathlessness score	3 (2 – 3)	3 (2.5 – 4)	0.25
COPD and Airways Assessment Test (CAAT) score	20 (14 – 25.25)	27 (22.5 – 32.25)	**0.004**
COPD Severity Assessment (GOLD) (%)			
GOLD A	2 (6)	0	**0.003**
GOLD B	20 (61)	3 (17)	**0.003**
GOLD E	11 (33)	15 (83)	**0.003**
Respiratory Medication (%)			
SABA	33 (100)	18 (100)	-
LABA/ICS	0	1 (6)	0.17
LAMA alone	0	1 (6)	0.17
LABA/LAMA**	10 (30)	1 (6)	**0.040**
LABA/LAMA/ICS**	21 (64)	15 (83)	0.14

*All participants had lung function within 3 years of the study. In some cases, the lung function post study start was taken as it was closest.

**Included patients on various combinations, but receiving all the medication ICS inhaled corticosteroids, LABA long acting beta agonist, LAMA long acting muscarinic antagonist, SABA short acting beta agonist

Table 4: Differences in physiological signals comparing the stable COPD group with the exacerbating group.

Physiological variability measure	Stable COPD groups	Exacerbating COPD Group	p-value
Heart Rate (HR) measures (n = 31 vs. 9)			
Mean HR (bpm)	71.04 (64.55 – 75.10)	74.22 (67.42 – 82.31)	0.35
cSDNN (ms)	179.40 (162.14 – 245.83)	268.41 (206.67 – 314.90)	**0.006**
SD1HR (ms)	7.80 (6.52 – 10.40)	12.06 (7.76 – 14.51)	**0.040**
SD2HR (ms)	74.76 (66.68 – 95.67)	90.18 (78.62 – 130.15)	**0.037**
SEHR	0.1607 (0.1355 – 0.1981)	0.1258 (0.1044 – 0.1568)	**0.015**
Respiratory Rate measures (RR) (n = 32 vs. 18)			
Mean RR (bpm)	16.86 (15.13 – 18.87)	18.58 (15.27 – 20.50)	0.30
SDBB (ms)	525.41 (398.08 – 665.35)	628.68 (514.90 – 1126.30)	**0.024**
SD1RR (ms)	91.97 (75.97 – 108.82)	133.61 (95.52 – 168.53)	**0.037**
SD2RR (ms)	737.48 (558.01 – 936.16)	875.93 (722.42 – 1584.36)	**0.025**
SERR	0.1078 (0.0743 – 0.1377)	0.1378 (0.0982 – 0.1916)	0.09
Airflow analysis (detrended fluctuation analysis) (n = 29 vs. 12)			
Alpha 1	1.6607 (1.6341 – 1.6730)	1.6294 (1.6055 – 1.6452)	**0.005**
Alpha 2	0.2805 (0.2600 – 0.3077)	0.2968 (0.2779 – 0.3110)	0.13
Alpha 3	0.6931 (0.6509 – 0.7931)	0.5000 (0.4676 – 0.5578)	**<0.001**

Median (IQR) shown. Mann Whitney U-test performed comparing stable COPD and exacerbating COPD population.

FIGURE LEGENDS

Figure 1: Study flow diagram

Figure 2: Heart rate multiscale entropy (MSE) comparing stable COPD participants and exacerbating participants

Figure 3: Respiratory rate multiscale entropy (MSE) comparing stable COPD participants and exacerbating participants

Figure 4: Variability analysis summary

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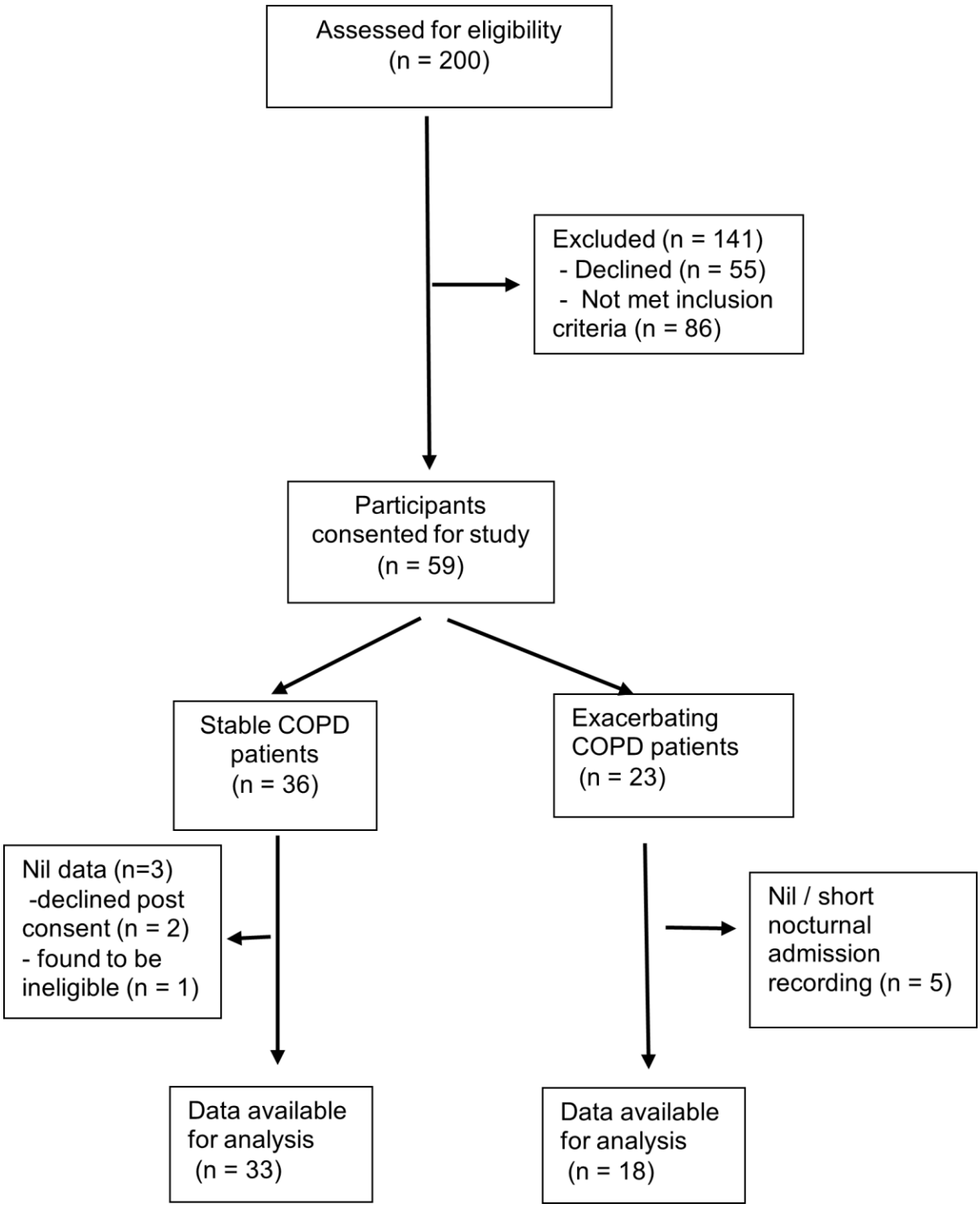


Figure 1

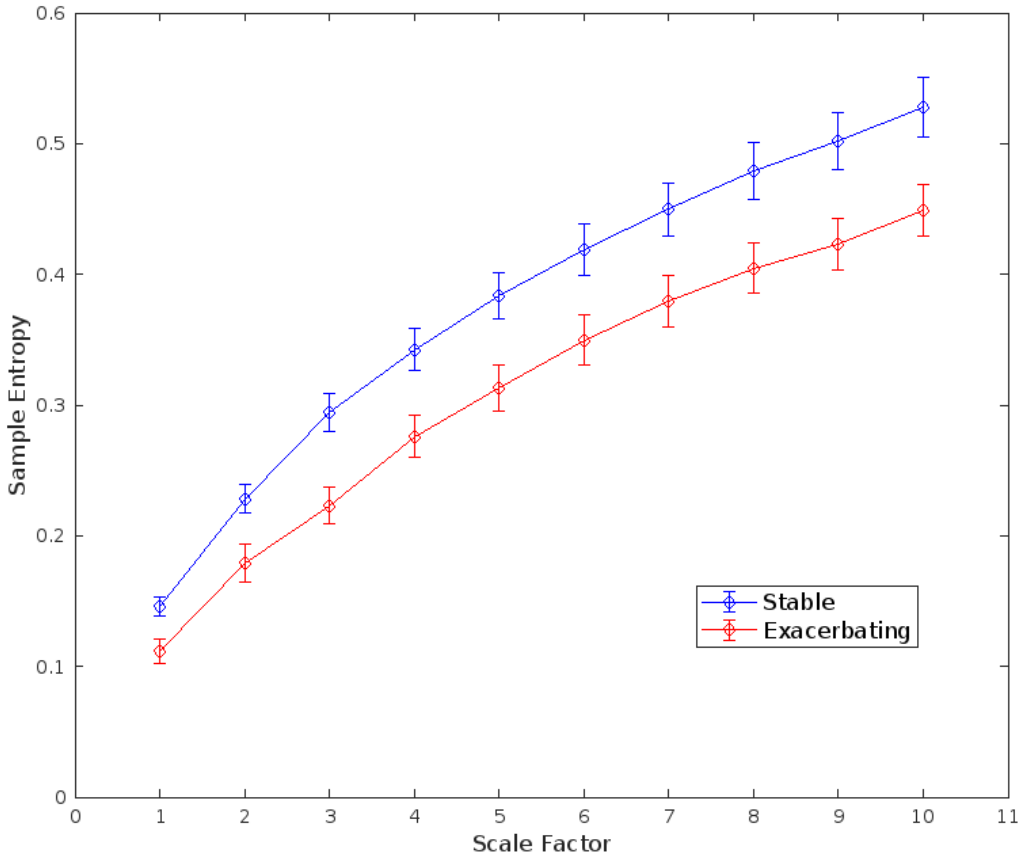


Figure 2

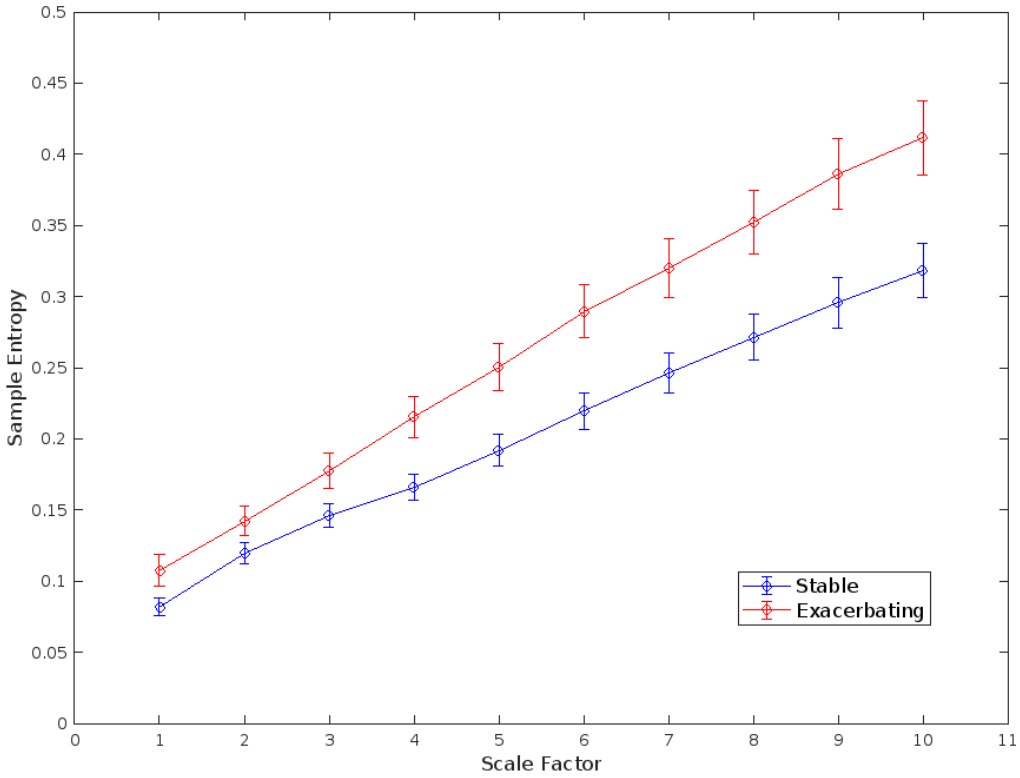


Figure 3

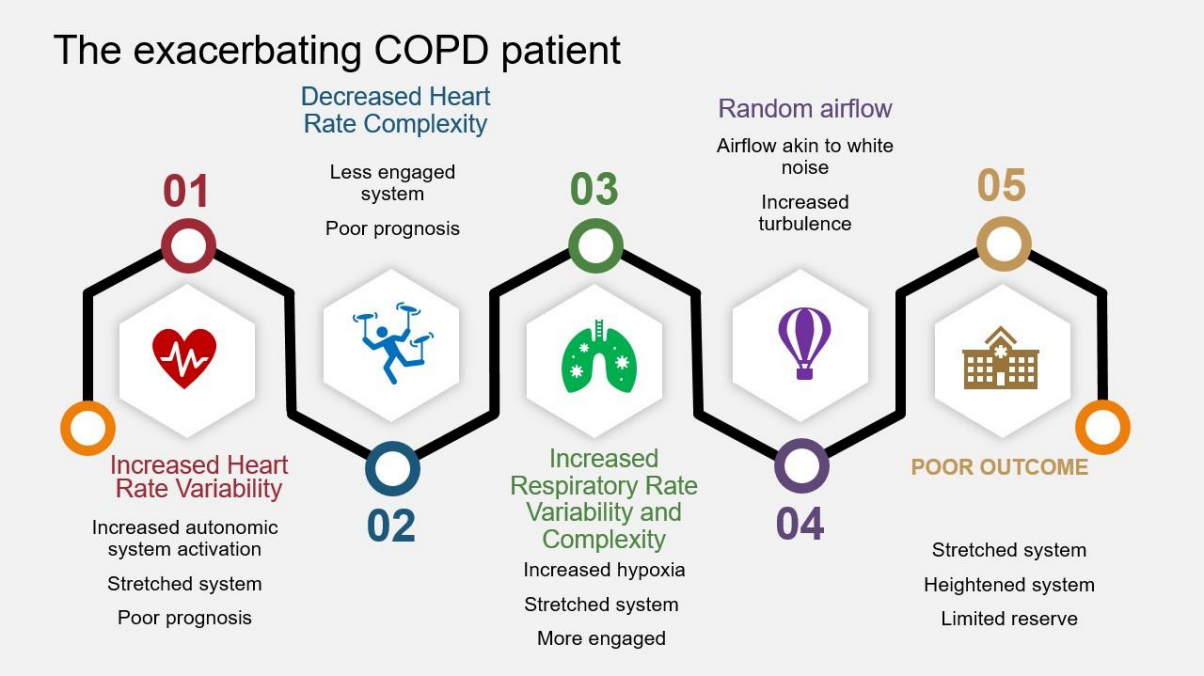


Figure 4

Heart rate, respiratory rate and airflow variability analysis in chronic obstructive pulmonary disease

Amar J Shah, Anita Saigal, Renard Pramono, Orsina Dessi, John R Hurst, Alireza Mani, Esther R Villegas, Swapna Mandal

Online Data Supplement

Contents

1. METHODOLOGY SUPPLEMENT

1.1 Wearable device

The wearable device used for this was AcuPebble RE100. Under the scope of this study, AcuPebble was not used as a medical device, but as an acoustic monitor to acquire signals, for which it is CE marked. AcuPebble RE100 is a small circular device and can be seen in Figure S1.

Figure S1: AcuPebble

Reproduced with permission from Acurable Ltd

AcuPebble RE100 attaches to the base of the neck to record various physiological acoustic signals including sounds generated from patient's respiratory and cardiac functions. These are then wirelessly transferred to a mobile device and uploaded to a GDPR compliant cloud.

Subsequent algorithms convert these sounds into three main physiological signals:

1. **Respiratory rate (breaths per minute)** measured every two seconds and validation work with Bland Altman plots have shown a RR bias of -0.215 breaths per minute (LOA between -5.747 to 5.316 breaths per minute). (Unpublished)
2. **Heart rate (beats per minute)** measured every two seconds and the root mean squared error (RMSE) of the heart rate, with the 50-120 beats per minute range is 3.62 beats per minute. (1)
3. **Airflow (normalised volt (V))** with a recording every 0.1seconds, giving 100 recordings every second.

1.2 Nocturnal time-window

There are limited data on nocturnal physiological variability analysis and currently no gold standard duration of analysis is recommended in the COPD population. However, previous work on heart rate variability has described long term (24 hours), short-term (5 minutes) and ultra-short-term (<5min) analysis, which are not interchangeable. It has also been recognised that longer term analysis will enable better representation of the overall response. (2) Therefore, when comparing nocturnal readings from several patients, a fixed time-series duration is necessary to avoid bias and improve comparability. Six hours was felt to adequately represent all the stages of sleep and give more than enough data points (10,800) to conduct physiological variability analysis. Studies with less than six hours of recording were deemed too short and excluded from the analysis. When patients had more than six hours of recording, only the first six hours were analysed (excluding the first 10minutes), so that the same time-series duration was used in all patients. If a time-series had ≥ 15% of data missing, this was excluded from the analysis.

The exacerbating group had recordings available throughout their stay (both day and night), however, for comparability, we chose to only use the nocturnal recording portion. To reduce bias, the median start time of all the stable valid six-hour nocturnal recordings was calculated and used as the start time for the exacerbating population. This was to ensure a similar time and duration of the recording, thus increasing comparability. The first valid nocturnal recording within 48 hours was used to compare with the stable group.

1.3 Linear analysis measures – heart rate and respiratory rate

The heart rate and respiratory rate was measured every two seconds by AcuPebble RE 100. For the duration of six hours, 10,800 data points were available to analyse. Given the large number of data points available for analysis, to deal with missing data, the data was first cleaned to remove potential artefact:

- Heart rate (HR) – any measurement below 40 beats per minute, was assumed to be inaccurate data capture, and this measurement was changed to the median HR.

- Respiratory rate (RR) – any measurement below eight breaths per minute was assumed to be inaccurate data capture, and this measurement was changed to the median RR.

The percentage of artefact for each trace was noted and if any recording had ≥15% of aberrant data, that study was not included in the final analysis. For included studies the following measurements were calculated.

The mean HR and RR was calculated. Successive R waves on an electrocardiogram (ECG) are denoted as the R-R interval. This is the interval between two successive heart beats. With the HR measurements the R-R interval (ms) was calculated by the following equation (3):

$$R - R\ interval = \frac{60{,}000}{HR}$$

With the RR measurements the breath-to-breath interval (B-B) (ms) was calculated by the following equation:

$$B - B\ interval = \frac{60{,}000}{RR}$$

Using both the R-R interval and B-B interval, the standard deviation of these intervals was calculated giving linear time-domain measure for each (SDNN and SDBB respectively).

Monfredi et al showed that the R-R interval (for HR) has an inverse non-linear relationship with HR and therefore ideally the SDNN should be corrected for the mean HR to reduce bias and improve reliability. This value (cSDNN) is shown in their equation below: (4)

$$\mathrm{cSDNN} = \frac{\mathrm{SDNN}}{e^{-\frac{HR}{58.8}}}$$

Therefore, for the HR data the cSDNN was also calculated. No such correction exists for the RR time series.

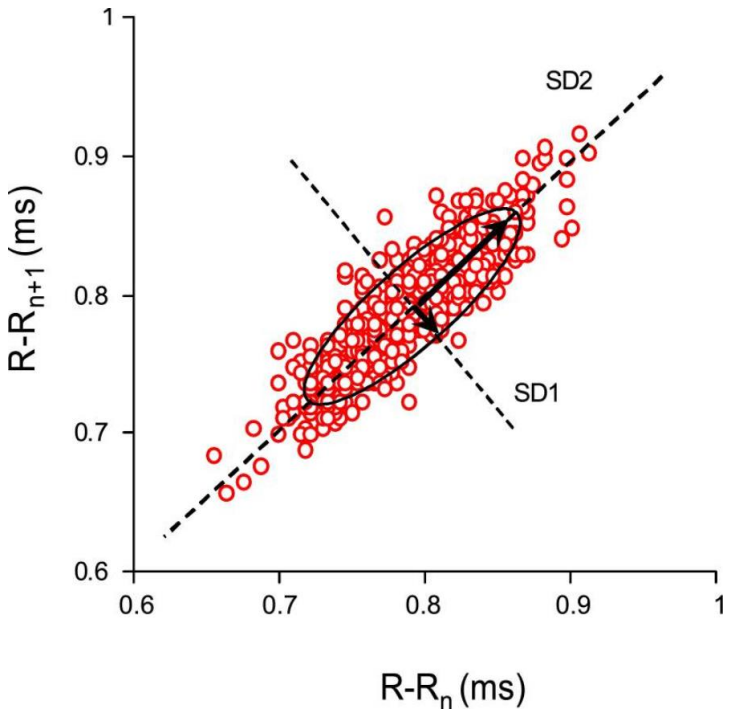
1.4 Non-linear analysis measures – heart rate and respiratory rate

For all non-linear analyses the calculated R-R and B-B intervals was used, rather than the original HR and RR time-series, as this is conventional methodology in the literature.

1.4.1 Poincare plots

A Poincare plot is a graphical representation (scatter graph) of the correlation between two consecutive data points in a time-series. For example, between two consecutive R-R intervals ($R\text{-}R_n$ and $R\text{-}R_{n+1}$). This is illustrated in Figure S2. An ellipse is subsequently fitted to the line of identity (the line where the x-value and y-values are equal). Two values are then calculated from this plot. SD1 is the standard deviation of the points perpendicular to the line of identify and SD2 is the standard deviation along the line of identify. SD1 represents shorter term fluctuations (beat-to-beat), while SD2 represents longer term fluctuations in the time series. (5, 6)

Figure S2 Poincare plot example (reproduced with permission from Mani et al (6))



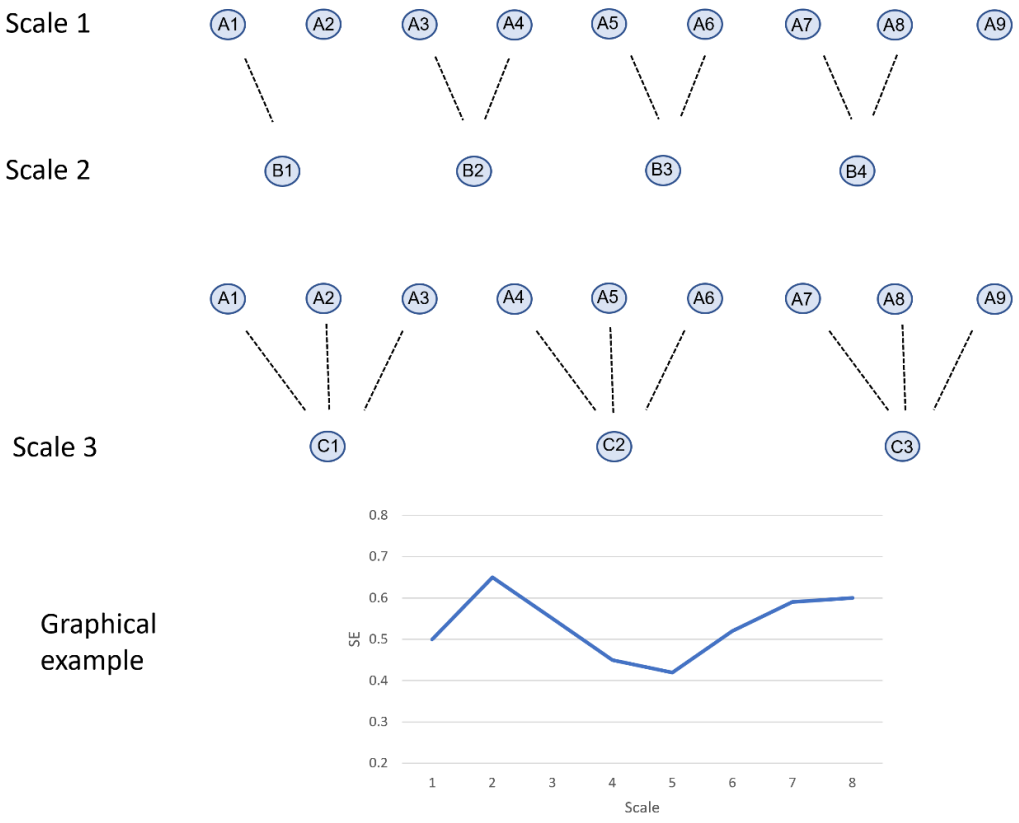
1.4.2 Sample entropy

Sample entropy measures the probability that sequences of a certain length (*m*) in a time-series is repeated at a later point, with a certain degree of tolerance (*r*). Tolerance (*r*) is akin to a confidence interval. Additionally, it measures whether this pattern of sequences of length *m*, remain similar when the next sample (*m*+1) is included in the sequence. Putting it simply SE quantifies the degree of irregularity vs. regularity in a time series. (7-9) Low values of SE suggest a greater degree of regularity and less complexity compared to higher values. SE, as a measure of complexity, will account for the interference from multiple regulatory systems affecting a time-series. (10-12) SE usually has no units ascribed to it

1.4.3 Multi-scale entropy

Multiscale entropy (MSE) is used to further define the richness of a time-series by taking into account the multiple scales that exist in physiological systems. It relies on calculating sample entropy over a range of different scales. The data is coarse grained or zoomed out. This concept is illustrated in Figure S3.

Figure S3 Multiscale entropy analysis. (Adapted from (13))



For SE calculations I used settings of *m* at 2 and *r* at 0.2. These values of m and r are widely used in the existing literature and are accepted as the standard.

Multi-scale entropy (MSE) was also calculated for both HR and RR using well described and freely available coding algorithms in MATLAB processing software. For this analysis, MSE was used over ten scales with *m* at 2 and *r* at 0.2.

1.5 Detrended fluctuation analysis: airflow data

The airflow data had a high resolution of 100Hz, meaning that there were 100 data points every second. Using the same six-hour window this gave us 2,160,000 data points. The data was initially cleaned to remove potential artefact. If there was a 30 second apnoea (determined by 3000 data points where the airflow was 0, this was deemed to be artefact and thus deleted.

Many physiological time-series have no characteristic length scale, exhibit long-range power-law correlations, are self-affine and are non-stationary. DFA accurately quantifies long-range power law correlations of a non-stationary time series, providing a quantitative parameter, known as the scaling exponent (α) which is akin to the fractal dimension. (14, 15)

While the mathematics is complicated, DFA looks at the time-series at various scales, de-trends the data, by subtracting the local trend at each scale, and then calculates the fluctuation at each scale. The fluctuation is akin to the standard deviation. This computation is repeated several times and at different scales to provide a relationship between the fluctuation and the scale. This is plotted in a double logarithmic axis and the exponent of the straight line is α. The values of α have various meanings: (15)

- $\alpha = 0.5$ indicates white noise and completely random fluctuation
- $0.5 > \alpha < 1.0$ indicates positive autocorrelation, whereby, using heart rate, as an example one large inter-beat interval is followed by another large inter-beat interval.
- $\alpha < 0.5$ indicates anti-correlation, whereby for example one large inter-beat interval is followed by a short inter-beat interval.

It is important to note, that in physiological time-series the scaling component is not always constant (independent of scale) and therefore crossovers often exist. This

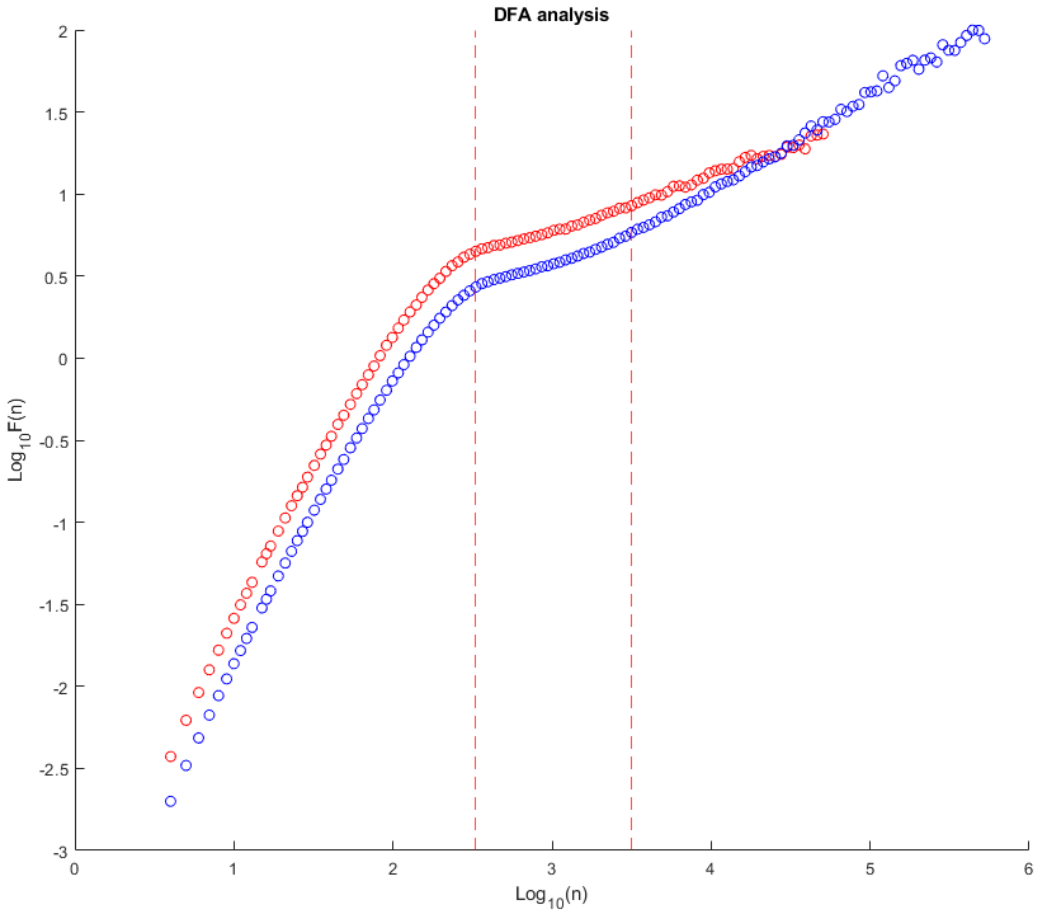
means the scaling component (α) differs for different ranges of scales. This is usually due to a change in the correlation properties of the signal at different time scales. (16)

Previous studies have shown that both oxygen saturation and heart rate (15) DFA graphs have one ‘cross-over’ point. Initial analysis of our airflow data showed two ‘cross-over’ points suggesting a short-term, intermediate term and long-term scaling exponent, α1, α2 and α3 respectively. These were calculated separately by visually inspecting the DFA graph and identifying the cross-over point manually. The first three airflow recordings for the first five patients (total of 15 recordings) were all inspected manually and found to have similar cross-over points. Two cross-over were also seen in preliminary analysis of the exacerbation COPD population and the points were the same as the stable population, allowing for direct comparison.

It is useful to note, that the first cross over point at a scale of 2.52114 is equivalent to $Log_{10}(332)$ and means that we are looking at the data at a scale of roughly 3 seconds (as we have 100 data points every second). Therefore, α1 is a short-term scaling exponent. The second cross-over point at a scale of 3.49941 is equivalent to $Log_{10}(3158)$ and means that we are looking at the data at a scale of roughly 31 seconds, therefore α2 is an intermediate scaling exponent and there after α3 is a longer scale scaling exponent.

An example of DFA analysis of a single night from a stable COPD participant and an exacerbating participant demonstrating the 2 cross-over points can be seen in Figure S3.

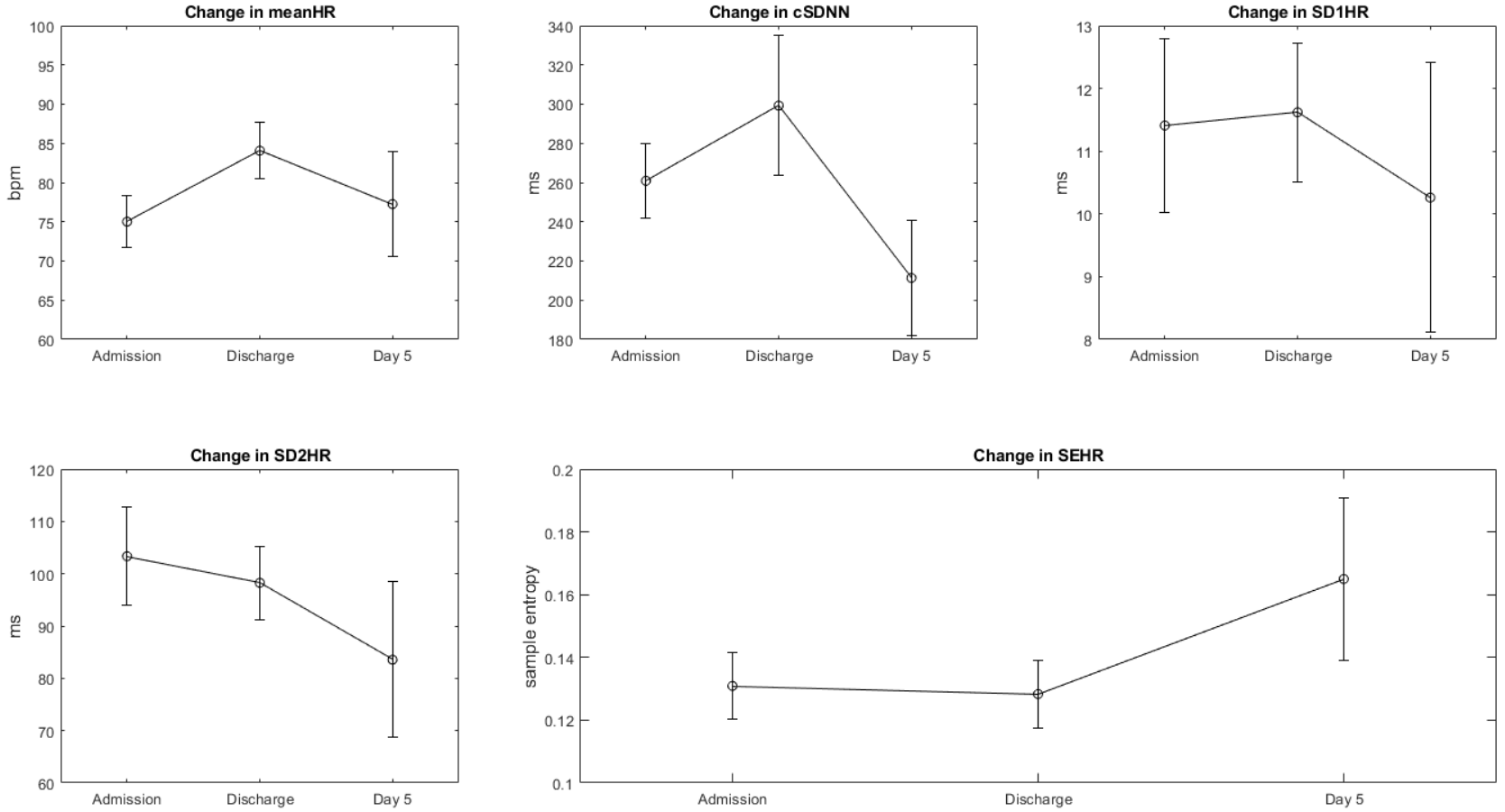
Figure S3: Detrended fluctuation analysis of a single night from a stable COPD participant and an exacerbating participant



Exacerbating patients represented by red circles and stable by blue circles. The dotted vertical lines represent the cross-over points

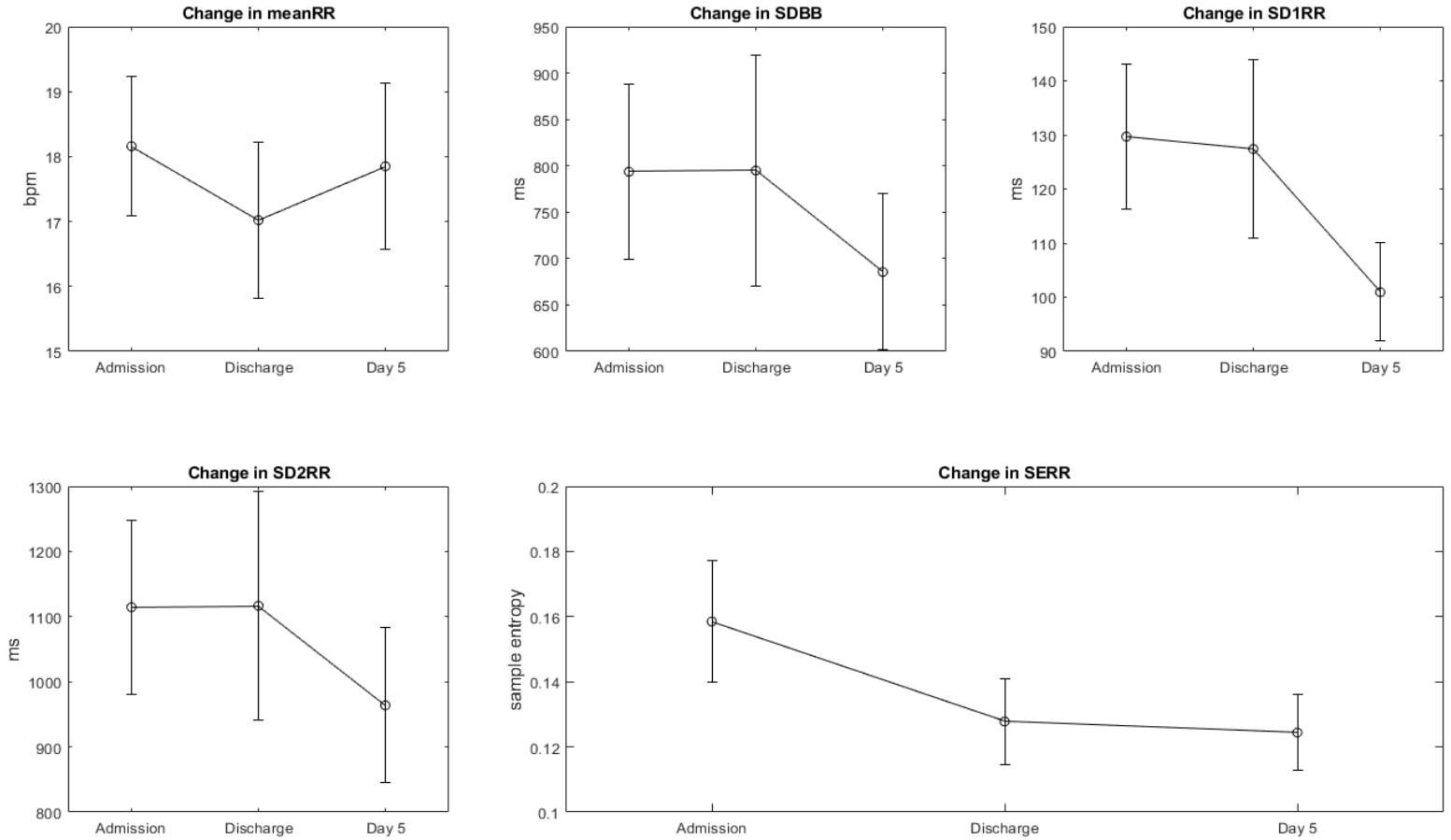
2. Exacerbating participants: admission vs. 5-days post discharge

Figure S4: Heart rate variability measures at admission, discharge and 5-days post discharge



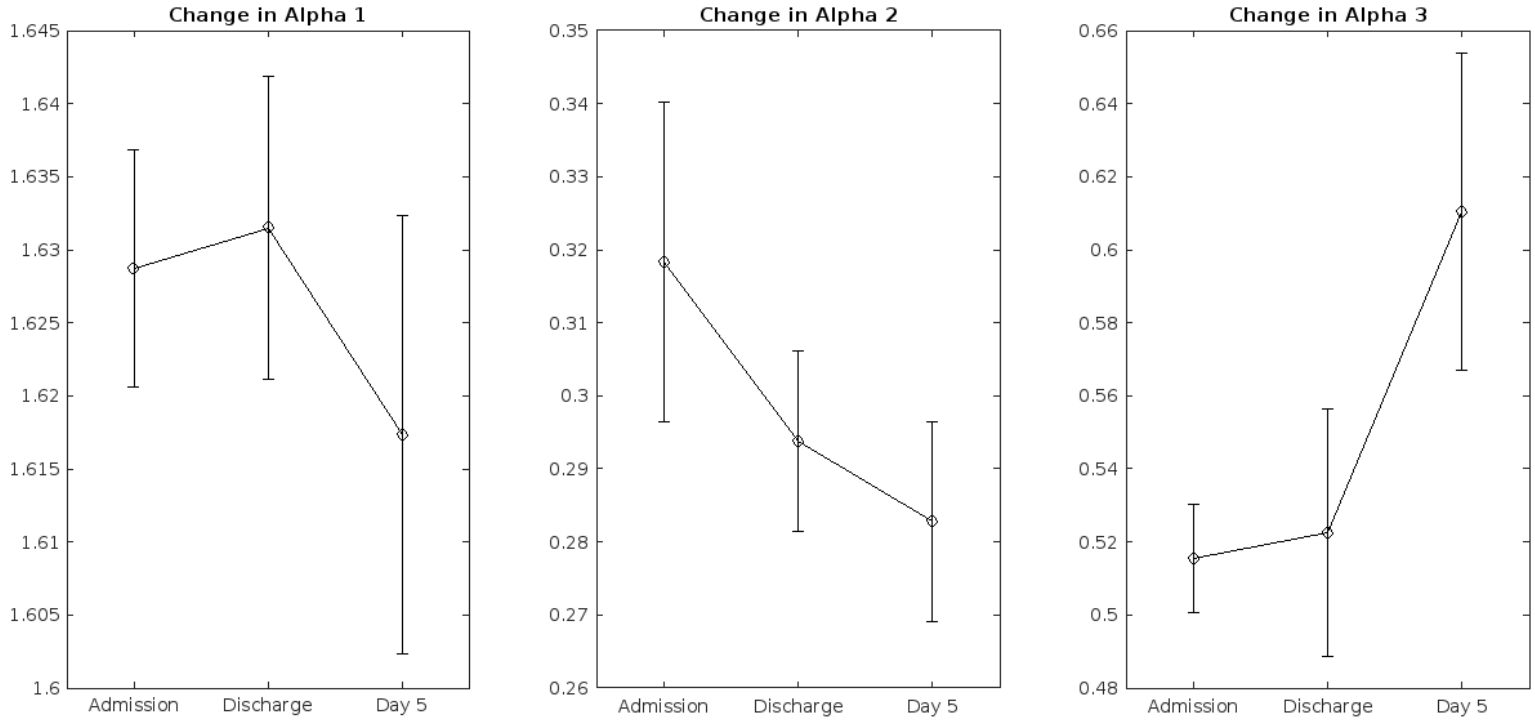
Circles represent the mean value and error bars represent the standard error.

Figure S5: Respiratory rate variability measures at admission, discharge and 5-days post discharge



Circles represent the mean value and error bars represent the standard error.

Figure S6: Airflow measures at admission, discharge and 5-days post discharge



Circles represent the mean value and error bars represent the standard error.

Figure S7: Multi-scale entropy analysis of heart rate time-series at admission, discharge and 5-days post discharge

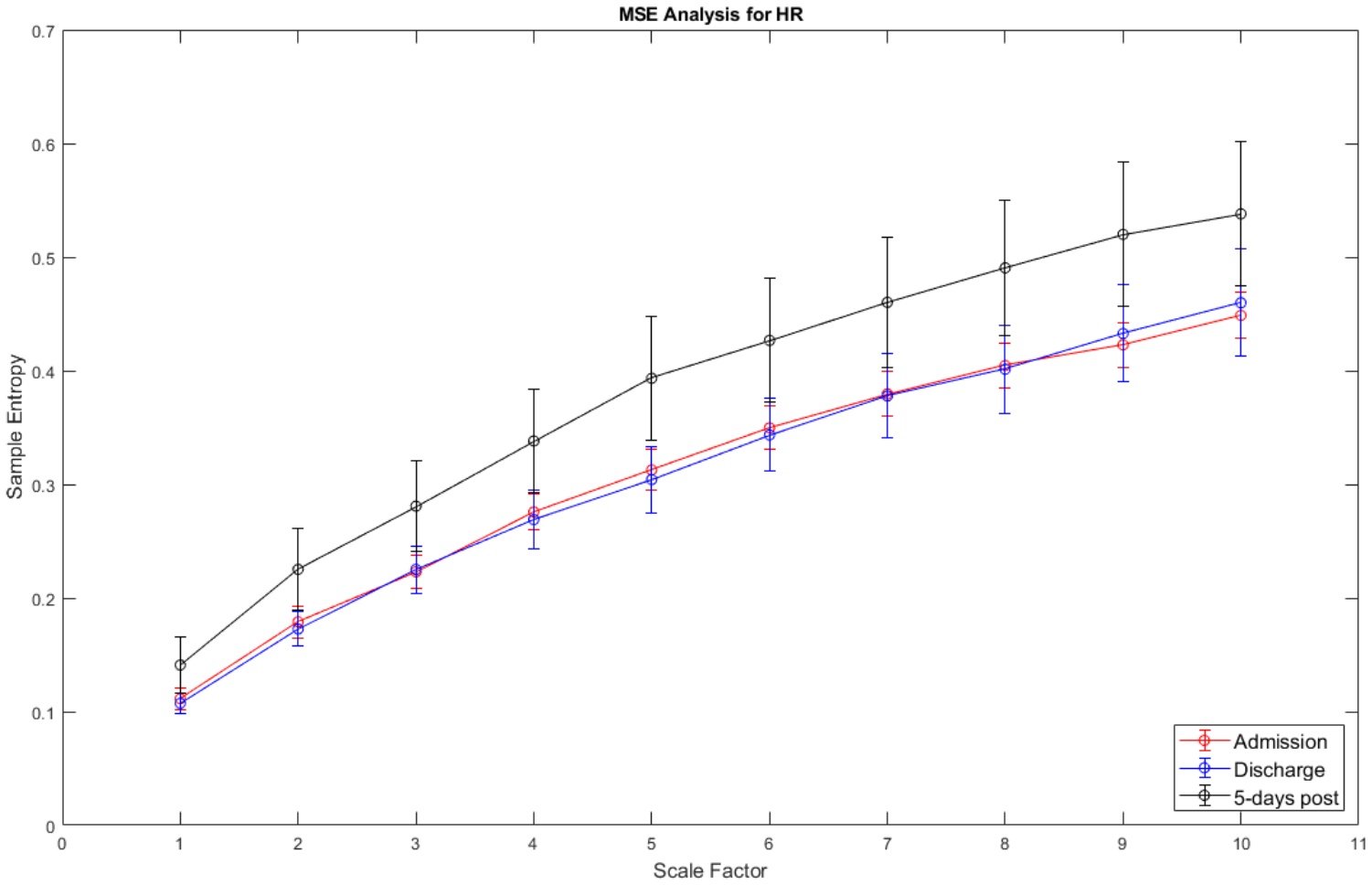
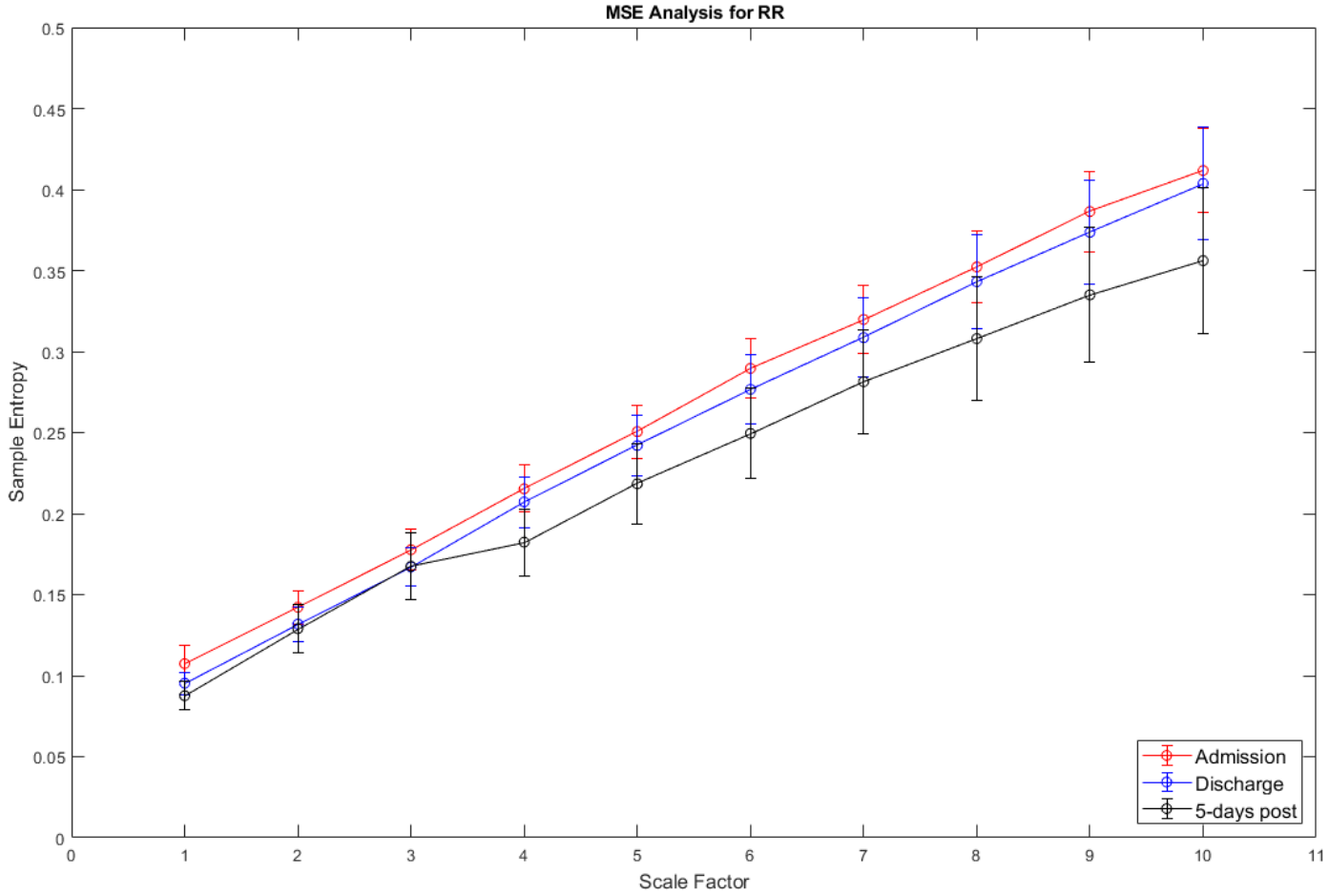


Figure S8: Multi-scale entropy analysis of respiratory rate time-series at admission, discharge and 5-days post discharge.



3. Historical non-COPD group

Given the novel findings of this work, as a point of reference for the reader, we include some data from a historical non-COPD group. We have data on a historical cohort of patients without COPD who used AcuPebble SA100, a similar device to AcuPebble RE100 which works in the same way. This data was part of a previous study by our group validating AcuPebble SA100 for sleep apnoea diagnostics. (17) Patients with a normal sleep study and therefore no sleep apnoea were defined as having an apnoea/hypopnoea index of <5events/hr. Their heart rate, respiratory rate and airflow time-series data was extracted and analysed using the same algorithms and methodology described above. As for the stable patients, a six-hour nocturnal recording was used (excluding the first 10-minutes) giving the same number of data points.

The results presented below show the baseline characteristics of the non-COPD, the physiological signal variability measures and the multiscale entropy measurements for the non-COPD group, in context with stable and exacerbating participants.

Table S1: Baseline characteristics of non-COPD group vs. stable vs. exacerbating participants.

Baseline characteristic	Non-COPD group (n = 51)	Stable COPD (n = 33)	Exacerbating COPD (n = 18)	p value*
Male (%)	29 (57)	20 (61)	10 (56)	0.73
Female (%)	22 (43)	13 (39)	8 (44)	0.73
Age (years) (mean ± SD)	38 ± 11	67 ± 10	64 ± 9	0.46
Body Mass Index ($kg.m^2$) (median (IQR))	25.2 (23.5 – 28.9)	27.1 (21.0 – 31.8)	18.9 (17.7 – 24.5)	**0.002**
Current smoker (%)	8 (15)	6 (18)	7 (39)	0.11
Ex-smoker (%)	12 (24)	27 (82)	11 (61)	0.11
Pack year history (median (IQR))	-	47 (25 – 64)	43 (40 – 50)	0.97
Mobility (%) • Independent • Uses a stick • Uses a frame	-	 • 20 (61) • 11 (33) • 2 (6)	 • 13 (72) • 4 (22) • 1 (6)	0.69
Independent with regards to activities of daily living (%)	-	31 (94)	18 (100)	0.29
Medical Co-morbidities (%)				
Alpha-1 Antitrypsin	0	4 (12)	0	0.12
Atrial fibrillation	0	3 (9)	0	0.19
Cerebrovascular disease	0	0	0	-
Hypercholesterolaemia	1 (2)	9 (27)	5 (28)	0.97
Hypertension	5 (10)	11 (33)	5 (28)	0.68
Ischaemic heart disease	1 (2)	5 (15)	2 (11)	0.69
Oxygen therapy	0	2 (6)	1 (6)	0.94
Peripheral vascular disease	0	1 (3)	0	0.46
Type 2 diabetes mellitus	1 (2)	5 (15)	1 (6)	0.31

*p value represents differences between stable COPD and exacerbating COPD participants

Table S2: Differences in physiological signals comparing non-COPD group vs. stable COPD group vs. exacerbating group.

Physiological variability measure	Non-COPD group	Stable COPD group	Exacerbating COPD group	p-value[b]
Heart Rate (HR) measures (n = 31 vs. 9)				
Mean HR (bpm)	65.48[a] (60.83 – 70.03)	71.04 (64.55 – 75.10)	74.22 (67.42 – 82.31)	0.35
cSDNN (ms)	189.43 (147.92 – 244.59)	179.40 (162.14 – 245.83)	268.41 (206.67 – 314.90)	**0.006**
SD1HR (ms)	8.90 (6.92 – 10.38)	7.80 (6.52 – 10.40)	12.06 (7.76 – 14.51)	**0.040**
SD2HR (ms)	87.61 (65.73 – 115.35)	74.76 (66.68 – 95.67)	90.18 (78.62 – 130.15)	**0.037**
SEHR	0.1872 (0.1273 – 0.2307)	0.1607 (0.1355 – 0.1981)	0.1258 (0.1044 – 0.1568)	**0.015**
Respiratory Rate measures (RR) (n = 32 vs. 18)				
Mean RR (bpm)	15.67[a] (14.26 – 17.00)	16.86 (15.13 – 18.87)	18.58 (15.27 – 20.50)	0.30
SDBB (ms)	478.98 (349.30 – 654.93)	525.41 (398.08 – 665.35)	628.68 (514.90 – 1126.30)	**0.024**
SD1RR (ms)	88.93 (69.59 – 126.41)	91.97 (75.97 – 108.82)	133.61 (95.52 – 168.53)	**0.037**
SD2RR (ms)	672.144 (488.23 – 916.01)	737.48 (558.01 – 936.16)	875.93 (722.42 – 1584.36)	**0.025**
SERR	0.0906 (0.0533 – 0.1347)	0.1078 (0.0743 – 0.1377)	0.1378 (0.0982 – 0.1916)	0.09
Airflow analysis (detrended fluctuation analysis) (n = 29 vs. 12)				
Alpha 1	1.6751[a] (1.6601 – 1.6820)	1.6607 (1.6341 – 1.6730)	1.6294 (1.6055 – 1.6452)	**0.005**
Alpha 2	0.2367[a] (0.2070 – 0.2661)	0.2805 (0.2600 – 0.3077)	0.2968 (0.2779 – 0.3110)	0.13
Alpha 3	0.7191 (0.6608 – 0.7762)	0.6931 (0.6509 – 0.7931)	0.5000 (0.4676 – 0.5578)	**<0.001**

Median (IQR) shown. [a]represents significant differences between the healthy population and stable COPD. [b]Mann Whitney U-test performed comparing stable COPD and exacerbating COPD population.

Figure S9: Heart rate multiscale entropy (MSE) comparing non-COPD group, stable COPD participants and exacerbating participants.

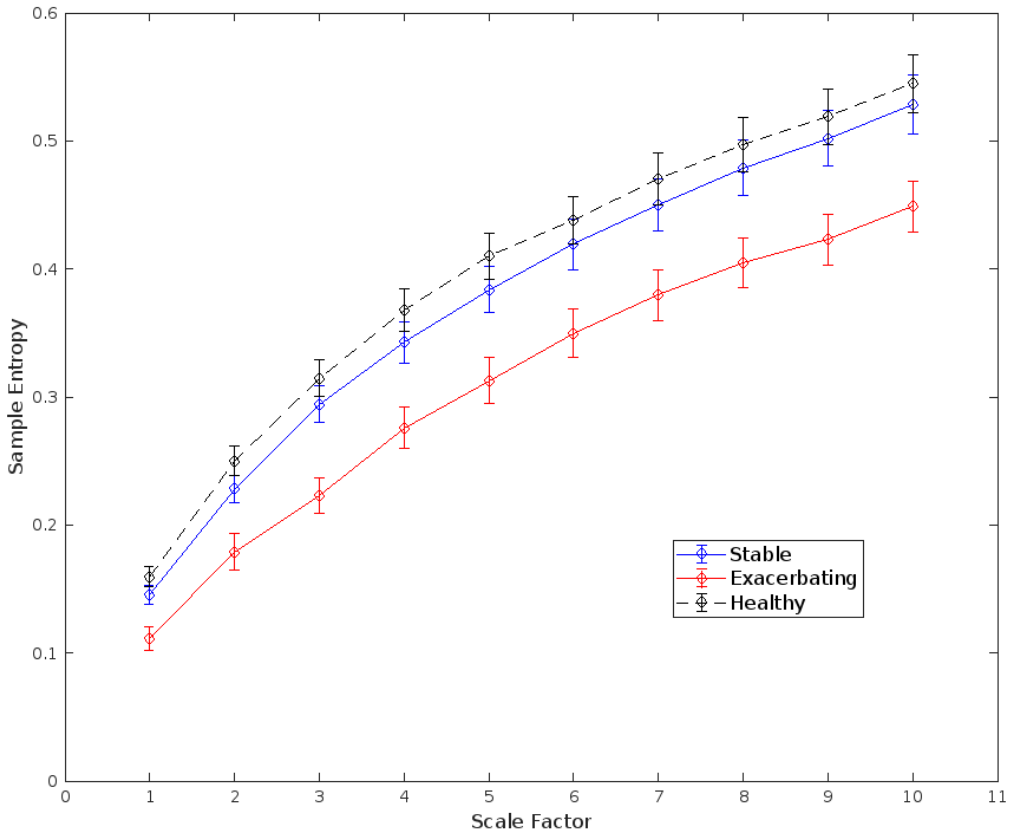
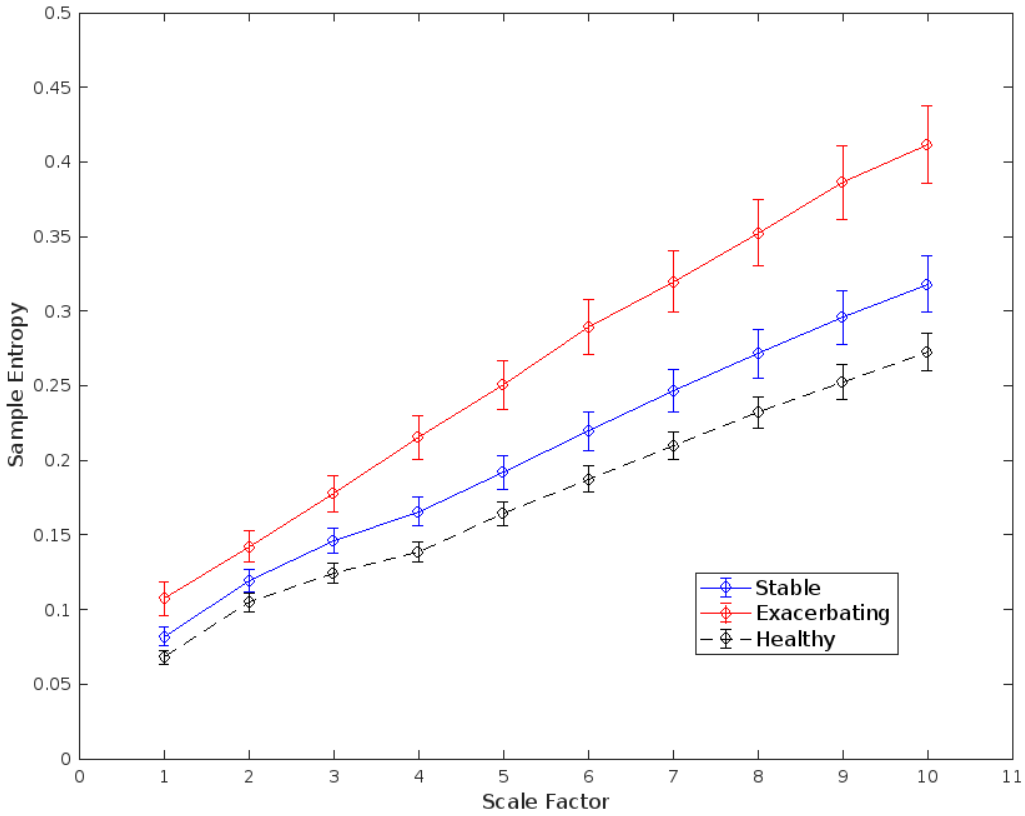


Figure S10: Respiratory rate multiscale entropy (MSE) comparing non-COPD group, stable COPD participants and exacerbating participants.



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