Early View

Research letter

**Novel breathing pattern analysis: Symmetric Projection Attractor Reconstruction (SPAR) improves identification of impending COPD re-exacerbations. A retrospective cohort analysis**

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Novel breathing pattern analysis: Symmetric Projection Attractor Reconstruction (SPAR) improves identification of impending COPD re-exacerbations. A retrospective cohort analysis.

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To the editor:

Acute exacerbations of COPD (AECOPD) are the second most common cause of emergency hospitalisation worldwide, with one-quarter of patients readmitted within 30 days of discharge [1]. Each exacerbation accelerates lung function decline [2] and is associated with a deterioration in health-related quality of life and an increased risk of mortality in the post-discharge period [3]. Several pathophysiological changes including decreased peak expiratory flow rate and increased dyspnoea often occur in the 3-5 days preceding an exacerbation [4]. This time window presents an opportunity to identify AECOPD, initiate patient self-management and clinical interventions aimed at mitigating hospitalisation. Sensitive and specific biomarkers of physiological stress, which can be easily applied and interpreted in both community and clinical settings, would facilitate earlier identification of AECOPD.

Increased respiratory rate (RR) is a well-validated biomarker of respiratory stress that is often incorporated into patient monitoring systems, facilitating early identification of deterioration [5]. Respiratory pressure/flow/plethysmography/thermistor waveforms are typically sampled as high-fidelity time-series data (~100-1000 Hz) and RR measurement automated to circumvent common inconsistencies with manual breath counting, using algorithms to detect waveform peaks [6]. However, such analysis disregards the intermediate data points which contain information about changes in waveform morphology, quantification of which could also help to identify physiological change. Symmetric Projection Attractor Reconstruction (SPAR) - a novel analysis technique, overcomes this problem. SPAR replots every data point of any cyclic waveform, generating a new visual representation (‘attractor’). Quantifiable attractor features can be extracted, providing new diagnostic metrics pertaining to waveform morphology [7]. SPAR is resistant to baseline wander and has previously been successfully applied to cardiovascular waveforms [8]–[10].

The objective of this study was to apply SPAR to respiratory waveforms from patients recovering from severe AECOPD. We hypothesised that SPAR would generate more sensitive biomarkers of impending COPD re-exacerbations compared to RR.

We performed a retrospective secondary analysis from raw nasal pressure waveform data (sampled at 512 Hz) initially collected to evaluate the trajectory parasternal electromyogram (EMG) changes in patients recovering from an AECOPD (NCT03443505) [11]. Waveforms were recorded during six minutes of resting breathing at hospital discharge and then daily in the patient’s home over a 30-day period post-discharge. Time-series data were processed in a blinded manner to avoid bias; 2 patient datasets were excluded, based on unfavourable signal-to-noise ratios.

Our secondary analysis subdivided patients into two groups: ‘stable’ and ‘re-exacerbating’. The six ‘stable’ patients remained at home for 30 days. Of the four re-exacerbating patients, two were readmitted to hospital on day 2 post-discharge, and 2 patients self-administered a rescue pack of corticosteroids and antibiotics on days 23 and 30, with the former patient hospitalised on day 24.

Concomitant respiratory medications were balanced between both groups, except for carbocisteine which was used by 4/4 patients in the re-exacerbating group vs. 2/6 in the stable group.

Waveform analysis was performed using a bespoke MATLAB software tool (MATLAB version 2022b). This program enabled the management and visualisation of waveform time-series data, and the generation and quantification of SPAR attractors. The SPAR method [7], [8], replots a window of time-series cyclic data into 3-dimensional phase space and then projects this down one line, to generate a 2-dimensional attractor. Attractors visually amplify small morphological changes from the original waveform.

Multiple visual attractor features were quantified using secondary algorithms. Our analysis revealed, the attractor’s ‘openness’ was the most visually distinct feature. To quantify this, we measured their 5% radial
opening (‘SPAR-Opening’). This metric conceptually equates to the relative size of a concentric growing circle until it covers 5% of the attractor – the more open the attractor, the larger the value. The conventional metric RR was separately quantified using the MATLAB Breathmetrics Package [12]. Wilcoxon rank sum tests or Chi-squared tests (where appropriate) were used to compare baseline characteristics between groups (p<0.05 was considered statistically significant). Univariate logistic regression models, using the described groups as outcomes, were generated for RR and SPAR-opening at different time points. Internal validation of these models allowed the comparison between the classification performances of these two metrics. Receiver Operator Characteristic Area Under the Curve (ROC-AUC) values quantified these performances, which ranged from 0.5 (poor discriminator) to 1.0 (perfect discriminator).

Other than increased pack years in re-exacerbating patients, there was no statistically significant difference in baseline characteristics between the two groups (Panel 1a). From the point of discharge, an opening was noticeable in the centre of the attractors from re-exacerbating patients, which enlarged in a time-dependent manner during the home-monitoring period, until hospital readmission/community treatment. In contrast, stable patients presented closed, helicopter-like attractors throughout (Panel 1b). Quantification of SPAR-opening reflected these observed changes (Panel 1c). The conventional metric, RR, was also elevated in re-exacerbating patients throughout the monitoring period, as expected (Panel 1c). However, SPAR-opening outperformed RR, reflected by increased ROC AUC values from the day of discharge (RR 0.92 vs SPAR 1.00) and throughout the 30-day home-monitoring period (RR 0.8-0.89 vs. SPAR 0.98-1.0) (Panel 1c).

In-silico modelling revealed that SPAR-opening quantified the bilateral symmetry of the inspiratory and expiratory waveform segments (Panel 1d). As the waveform became more symmetric, the centre of the corresponding attractor gradually opened, positively correlating with a future exacerbation. In stable COPD patients, the waveform fraction for inspiration was approximately 1/3rd of the whole breath cycle length, but the inspiratory and expiratory times equalised in the re-exacerbating patients. SPAR-opening quantified this duty-cycle change, but additionally quantified the overall increased symmetry of the entire waveform’s morphology. This increased symmetry is unlikely to be specific for AECOPD but, rather, reflects a pathological change in the work of breathing.

This proof-of-concept study introduces a novel metric that is sensitive to physiological change, identified by analysing the morphology of raw nasal pressure waveforms. Our findings indicate that SPAR has potential clinical utility for earlier and more accurate recognition of AECOPD from resting tidal breathing. Whilst RR is an important biomarker, RR extraction by peak detection can be compromised in noisy data and is a reductionist analysis of the complex waveform signal. In contrast, SPAR faithfully utilises every waveform data point limiting inadvertent bias introduction, quantifying the entire breathing pattern, and, in this study, improved classification accuracy. Characterising waveform morphology to add diagnostic sensitivity is not in itself new, and has been applied to cardiovascular waveforms over decades, using other analytical techniques [13]–[15]. This current study applied SPAR, for the first time, to the lesser-studied respiratory waveform morphology.

A technological key discriminator is that, in addition to quantifiable metrics, SPAR generates images encapsulating and amplifying time-dependent waveform changes, at-a-glance. This can facilitate the visualisation of trends in patient status that may be less obvious when appraising waveform real-time traces directly. This visualisation aspect also opens opportunities to apply deep-learning image analysis methods, as are currently used for clinical imaging data, to support classification and alerts. Whilst the nasal pressure waveform data used in this study is not routine, SPAR can be extended to clinically used methods where cyclic respiratory time-series data are acquired (e.g. thermistor, impedance plethysmography, non-contact chest motion technologies), as it is agonistic to signal type.

This proof-of-concept study will require larger validation studies, but the time-dependent changes in SPAR-opening, seen in all re-exacerbating patients, and entirely absent in stable patients, increase our confidence in
the metric’s value. Future research is now needed to explore the utility of combining SPAR metrics with established clinical biomarkers, including RR, to support clinical decision-making during both in- and outpatient care.

Figure 1

PANEL a) Baseline characteristics of studied patients, by group. Column labels indicate corresponding sample sizes. Age Range = median years age range. BMI (kg/m²), pack-years and EXACT (Exacerbations of Chronic Pulmonary Disease Tool) score at admission are shown as median and inter-quartile ranges. Last column shows p-values of a Chi-square ($x^2$) or Wilcoxon rank sum (w) test, comparing frequencies or median values of both groups, performed in MATLAB (MathWorks Ltd.) Panel b) 60-second SPAR attractors of 4 different COPD patients, 2 stable (top) and 2 re-exacerbating (bottom) over the monitoring period (columns represent the approximate day of monitoring). o = start of attractor opening. Panel c) Trajectories of RR and SPAR-Opening metrics over the 30-day monitoring period (median + IQR error bars) Red circles (re-exacerbating); blue triangles (stable). Tables below graphs indicate ROC AUC classification performance values of the corresponding metrics during the different stages of the monitoring period (D = days). Panel d) From left to right: example traces (60s, $\pm$ 0.5mV, inhalation shown below dotted line), attractors (60s, arbitrary units, size normalised) of day 2 recordings of a stable (top) and re-exacerbating (bottom) patient, in-silico modelling of traces (arbitrary units) and attractors (arbitrary units) replicating changes observed in the two different groups.
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Conflicts of interest:
MN and PJA are coinventors of SPAR method- Delay coordinate analysis of periodic data. WO2015121679A1 used in this study.

NH is involved in an investigator led/industry funded trial (unrestricted grant) with Resmed. He receives consulting fees from Philips for a hospital patient monitoring programme. He has received payments and honoraria from Fisher and Paykel (chairing ERS 2022 symposium) and Philips (Lecturing ERS 2022 symposium). He has received financial support for attending meetings from Fisher and Paykel (ERC 2022). He has patents planned, issued or pending for Myotrace (held by Guy’s and Thomas’ Foundation Trust).

RD receives consulting fees from Resmed and Astra Zeneca. She receives payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Fisher Paykel and Resmed. She receives support for attending meetings from Fisher Paykel and Resmed

MSP, MV, CJ, GR and JS have declared no conflict of interest.

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References


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