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Short Communication

Cosinor Analysis of Circadian Rhythm of Peak Expiratory Flow in Young Adults

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Abstract

Introduction: Peak expiratory flow (PEF), exhibit a 24 hour circadian rhythm with nadir in the early morning and peak in the evening. This diurnal variability gets accentuated in asthmatics. Rhythm characteristics of such time series data can be better explained using Cosinor analysis by fitting a cosine curve. Also it makes easier to compare data even when there is a difference in sampling time points. Data of PEF circadian rhythms in Indian population with Cosinor analysis is lacking making it difficult to frame guideline to diagnose asthma.

Methods: PEF was recorded from 249 subjects using Wright's portable Peak Flow Rate meter at 5:00, 8:00, 11:00, 14:00, 17:00, 20:00, and 23:00 hours for one day. Cosinor analysis was done and rhythm characteristics were determined for individual subjects.

Results: The mean PEF values after a minimum in morning at 05:00 hours tend to increase throughout the day peaking in afternoon and there is a regular fall in PEF levels after 17:00 hours till 05:00 hours. Mean diurnal variation expressed as amplitude percent mean (A%M)is 8.81±4.8. With Cosinor analysis significant rhythms were detectable in 64% of subjects. For this population MESOR (Midline Estimate Statistic of Rhythm) is 528.49 L/min, Amplitude is 8.2% and acrophase is 15.49 Hours.

Conclusion: Results are comparable with the data published in other studies for other populations. The variability (amplitude) in normal subjects is lesser than that of smokers and asthmatics. Amplitude and acrophase characteristics will help unifying the data and guide in deciding the cut-off values for diagnosing asthma.

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Introduction

Peak expiratory flow (PEF), exhibit a dominant 24 hour circadian rhythm which follows a biphasic variation with nadir in the early morning and peak in

the evening (1, 2). This diurnal variability gets accentuated in asthmatics which explains worsening of symptoms of breathlessness in asthmatics in early morning hours and nocturnal asthma (3).

Over last several years different groups have provided data of PEF variability in various groups e.g. asthmatics, COPD, smokers, passive smokers, patients with ILD and also in normal subjects (2, 4, 5). National Heart Lung and Blood Institute (NHLBI) has advocated cut off limit of 20% for diagnosing asthma (6). But this is not found to be consistent (7). Using PEF variability the dilemma of cut-off values for diagnosing asthma is not yet resolved.

Methods used to analyse the PEF variability are not uniform across studies. Traditionally PEF variability is expressed as amplitude percent (8). The disadvantage of this approach is that timing of measurement and frequency of measurement limits the capacity to detect lowest and highest values. Moreover most of the studies have used only four to five times sampling of data over 24 hours, while it has been shown earlier that twice a day reading picks up only 20-45% of actual variability and readings 4 times a day can extract 60-80% of variability (9). Our group previously published PEF data collected over 7 times over a day from 42 healthy male subjects (10). It has been shown that rhythmometric analysis using Cosinor method for time series data can better explain the rhythm characteristics in terms of MESOR (Midline Statistic Of Rhythm, a rhythm-adjusted mean), amplitude (a measure of half the extent of predictable variation within a cycle) and acrophase (a measure of the time of maximum peak value) from the best fit cosine curve profile (11). Present study has tried to detect the circadian rhythm of PEF in normal subjects taking also into consideration the Cosinor method so that it can be compared across data from other populations.

Methods

Subjects

For this study 285 young male volunteers from university population following similar daily routine and similar sleep habits were recruited. Informed consent was obtained from each subject prior to participation in study. The participant information sheet and consent form were approved by institutional ethics committee.

A brief clinical history was taken and clinical examination of the subjects was performed to rule out any obvious cardio-pulmonary compromise. Subjects with history of smoking, history of severe chest trauma, with obvious chest and spinal deformity, with personal/family history of asthma, chronic obstructive pulmonary diseases and other cardio-respiratory diseases were excluded from the study.

Protocol

Study was done in small groups of 5-12 students and each group was provided one mini Wright's peak expiratory Flow Rate meter. Subjects were individually trained for measuring their own PEF in L/min. and were instructed to record the readings with Wright's portable peak Flow Rate meter at 5:00, 8:00, 11:00, 14:00, 17:00, 20:00, and 23:00 hours for one day. They were instructed to obtain at least three recordings at a time. Training was done day prior to actual recording and at least three out of seven sessions each day were under the guidance of the principal investigator and the remaining sessions were under the supervision of a trained subject chosen as group leader.

The data sheets were filled by subjects themselves and were asked to record PEF value for all three efforts. The pooled data sheets were scrutinized and those with incomplete test records or data were rejected. The best of three PEF readings in a given time was taken for the analysis. Finally, 249 subjects were selected for inclusion into the analysis.

Statistical analysis

Individual PEF values were normalized with day mean value for each individual subject to reduce the inter-individual differences. Normality of data and homogeneity of variance was tested with Shapiro-Wilk's test and Levene's test respectively.

PEF values were analysed by repeated measures

one way analysis of variance (ANOVA) followed by Tukey's HSD Post Hoc test.

Two indices amplitude percent mean (A%M) and standard deviation percent mean (SD%M) and were calculated for quantifying diurnal variation for individual subject (8).

PEF values were also analysed with single COSINOR method (11) using COSINOR code in MATLAB (12).

Results

PEF values of 249 male subjects with mean age of 21.1±2.2 years measured at 5:00, 8:00, 11:00, 14:00, 17:00, 20:00, and 23:00 hours were analysed. The mean PEF values after a minimum in morning at 05:00 hours tend to increase throughout the day peaking in afternoon as shown in Table I. The PEF measurement was not done at 02:00 hours, but there is a regular fall in PEF levels after 17:00 hours till 05:00 hours as per the trend depicted in Fig. 2.

The data was normally distributed and variance did not differ between different time points. The PEF values as well as their normalized means at different time points were analysed for variation using one

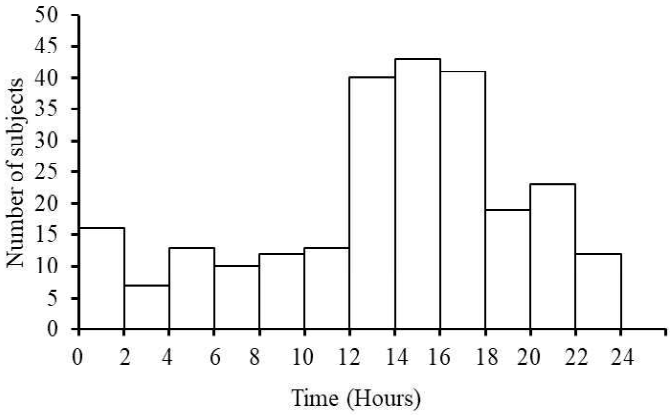

Fig. 1: Distribution of acrophase among subjects.

TABLE I: The mean PEF values and their standard deviations (SD) at various time points between 05:00 and 23:00 hours.

Time (Hours)	5:00	8:00	11:00	14:00	17:00	20:00	23:00
PEF (L/Min)	517.7*	525.6	535.4*	534.6*	534.0*	531.7	528.0
±SD	±55.7	±55.5	±54.2	±55.0	±54.4	±54.1	±54.3
Normalized PEF	97.7*	99.2*	101.1*	100.9*	100.8*	100.4*	99.7*
±SD	±4.1	±3.0	±2.9	±3.2	±2.8	±3.1	±3.2

Significant differences resulting from post hoc analysis are represented by *

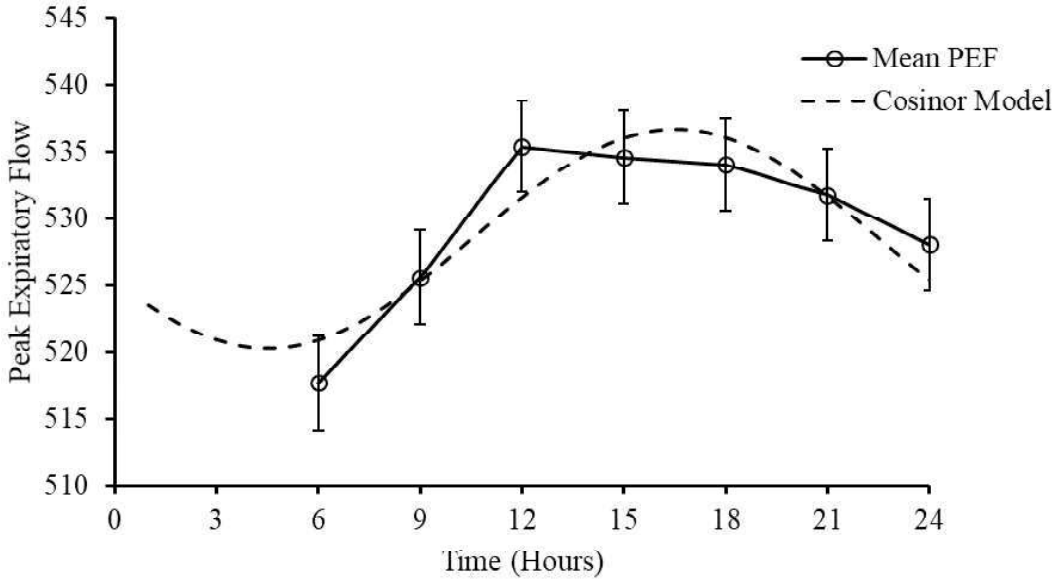

Fig. 2: Mean PEF values with error bars (standard error) at different time points and best fit cosine curve.

way analysis of variance which revealed statistically significant differences ($p<0.05$).Significant differences in the PEF values and normalized mean at various time points as has been shown in Table I.

Mean diurnal variation, was 8.81±4.8 (A%M) and 17.81±8.8 (SD%M) in this population. Significant Cosinor rhythm was detectable in 160 out of 249 subjects based on the zero amplitude test. Most of the subjects exhibited early morning decrease and afternoon rise in PEF. The distribution of acrophase among all subjects is presented in Fig. 1.

For determining group rhythm characteristics, mean PEF values at all time points were subjected to COSINOR analysis. The resulting acrophase is 15.49 Hours, Amplitude is 8.2% and MESOR is 528.49 L/min and SE of MESOR is 1.17. The resulting best fit cosine curve is shown in Fig. 2 along with mean PEF values curve.

Discussion

Cosinor analysis essentially is fitting a cosine curve assuming presence of rhythm in a given set of data. This method provide us with the mean value in the form of MESOR, estimate of diurnal variability in the form of amplitude from acrophase and bathyphase. Advantage of Cosinor analysis is that rhythm can even be estimated from relatively few data points (13).

The mean value of PEF by conventional analysis is 529.6±52.1 L/min which is comparable to MESOR value of 528.49 ± 52.10 L/min in our study. Similarly mean diurnal variation (A%M) and amplitude by Cosinor method are comparable (8.81 Vs 8.2%).

Cosinor rhythm was detectable in more than 64% subjects (160 out of 249) with amplitude of 8.2% in whole group with acrophase of 15.49 hours. The bathyphase (time corresponding to maximum dip in PEF) will be 12 hours opposite to acrophase and it correspond to the time of usual worsening of symptoms of breathlessness in asthmatics. Our results closely match with results of another study in which rhythm was detected in more than 65% of normal subjects (n=221) with amplitude of 8.3% & mean acrophase of 15.26 hours (1). Similar trends have been reported in a community study in children with detectable rhythm in approximately 50% of normal subjects (n=40) with amplitude of 4.2% & acrophase between 16-18 hours (14). Albertini et al. 1989, also reported detectable rhythm in 50% of normal subjects only (15). All three studies considered only 4 time points in a day however recording were done over 7 - 14 days. Troyanov et al. 1994, reported detectable rhythm in more than 50% of normal subjects measuring PEF at 8 times (5). Higher rhythm detection in our subjects may be due to more homogenous group with almost similar daily routine and living under similar living conditions.

Distribution of acrophase among subjects is quite similar to that reported by Hetzel et al. 1980 (1). In this study distribution of acrophase in subjects even without detectable rhythm was quite similar to those having significant rhythm, thus reflecting component of periodicity in them too.

Amplitude in our study is 8.2% which is similar to data published for normal subjects in the range of 5.9% to 8.3% in various other studies (1, 5, 14, 15). For asthmatic patients the value of amplitude % is higher, varying in different studies from 9.6% to 50.9% (1, 5, 14, 15). Thus Rhythm characteristics get exaggerated in Asthmatics which is also reflected by higher rhythm detection in these studies for Asthmatics.

The rhythm in airways reflects oscillations of control mechanisms regulating airways calibre. This gets exaggerated in subjects having bronchial hyper-reactivity or asthma with lowest values (bathyphase) in midnight or early morning.

For generating normative data, similar analysis of data from larger population of healthy subjects and diseased individuals is required for framing guidelines in Indian population. Also seasonal variations should be taken into account as it may affect the rhythm characteristics.

The cosinor analysis makes it easier to compare data from other studies even with difference in sampling at different time points. Amplitude and acrophase characteristics will help unifying the data

and better guide in deciding the cut-off values for diagnosing asthma.

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