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The Association of Cigarette Smoking with High Frequency Heart Rate Variability: An Ecological Momentary Assessment Study

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Abstract

Objective—Evidence from both laboratory and observational studies suggests that acute and chronic smoking leads to reduced high frequency heart rate variability (HF-HRV), a measure of cardiac vagal regulation. We utilized ecological momentary assessment (EMA) to study the effect of smoking on concurrent HF-HRV in a trial measuring the effects of hostility reduction, and compared 24-hour HF-HRV in smokers and non-smokers.

Method—Ambulatory ECG data were collected pre-randomization from 149 healthy, individuals with high hostility levels (20–45 years, BMI = 32 kg/m²) and paired with concurrent EMA ratings of smoking, and physical position during waking hours. A multilevel mixed model was estimated associating ln(HF-HRV) from smoking status (between-person factor) and person-centered momentary smoking (within-person factor, treated as a random effect), adjusting for momentary physical position, medication use, and consumption of alcohol and caffeine.

Results—35 smokers and 114 non-smokers provided both EMA and HF-HRV data. Within smokers, ln HF-HRV was reduced by 0.31 ms² ($p=0.04$) when participants reported having recently smoked cigarettes, compared to when they had not. The 24-hour HF-HRV was significantly lower in smokers (mean = $5.24 \pm \text{SD} = 0.14 \text{ ms}^2$) than non-smokers ($5.63 \pm 0.07 \text{ ms}^2$; $p=0.01$)."

Conclusion—In healthy, smokers with high hostility levels used as their own controls during daily living, smoking acutely reduced HF-HRV. HF-HRV was also reduced in smokers as compared to non-smokers. Although limited by a small sample of individuals with high hostility levels, these findings nonetheless provide additional evidence that cardiac vagal regulation is

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Conflicts of Interest

No conflicts of interest to report.

lowered by cigarette smoking, which may be one of the numerous pathophysiological effects of smoking.

Keywords

High Frequency Heart Rate Variability; Ecological Momentary Assessment; Cigarette Smoking; Hostility; Cardiac Vagal Regulation

INTRODUCTION

Cigarette smoking is associated with negative cardiovascular health effects and is one of the strongest risk factors for cardiovascular disease (CVD), stroke, peripheral vascular disease and congestive heart failure (CHF) (1). CVD complications such as myocardial infarction and sudden cardiac death have also been associated with active cigarette smoking (2, 3). Chronic cigarette smokers have an increased incidence of coronary artery spasm due to the vasoconstrictive effect that long-term cigarette smoking has on the coronary system (2). Long-term smoking has a harmful impact on blood pressure and sympathetic tone, as well as reducing myocardial oxygenation (4).

High frequency heart rate variability (HF-HRV), a measure of cardiac vagal control, is positively correlated with healthy cardiac function and longevity (5) whereas low HF-HRV predicts increased risk for all-cause mortality (6, 7) and mortality following a fatal myocardial infarction (8, 9). Several observational studies have reported the effects of chronic cigarette smoking on HRV in heavy smokers. Hayano et al. found that heavy smokers have lower vagal activation, assessed by HRV, than non-smokers (10). Barutcu et al. found reduced time domain parameters of HRV (standard deviation of normal to normal intervals; and root mean squared successive differences) in heavy smokers when compared to non-smokers (11).

Studies contrasting smokers and nonsmokers have produced sometimes contrasting findings. For example, Eryonucu et al. reported that more global time domain indices of HRV were lower in smokers compared to nonsmokers but that there were no differences in heart rate or RMSSD, a time domain index of high frequency HRV (12). In contrast, Alyan et al. found that LF power and the LF/HF ratio were greater in smokers compared with nonsmokers but HF power and SDNN and RMSSD were lower in smokers (13). Kupari et al. studied the effect of cigarette smoking on short-term HRV in a population free of heart disease and found that smoking was associated with a reduction of HRV (14). Molgaard et al. studied the effect of smoking in healthy participants, comparing heavy smokers, moderate smokers, and non-smokers, and found that smokers had lower total HRV during the daytime but not at nighttime (15). Lucini et al. compared HRV in 20 heavy cigarette smokers and 20 non-smoking volunteers of similar age and found significantly lower HF-HRV in the smokers, both when standing and at rest (16).

The acute effects of smoking on HRV have mainly been examined in laboratory studies. Hayano et al. measured HRV parameters in smokers before smoking a cigarette and at different short-time intervals (3, 10, 17 and 24 minutes) thereafter. They found a significant suppression of cardiac vagal control, reflected by reduced HF-HRV, 3 minutes after smoking

the cigarette (10). Similarly, other laboratory studies have shown reduced parasympathetic activity associated with active smoking (17, 18).

Both laboratory based and observational cross-sectional studies have several limitations when studying the effect of acute and chronic cigarette smoking on HRV. Observational epidemiological studies are limited by possible selection biases and also limited by their cross-sectional approach. Laboratory studies are limited by their lack of ecological validity.

We are aware of only a single, small study examining within-person relationships between cigarette smoking and HF-HRV in a natural living environment. Kobayashi et al. studied the acute effect of cigarette smoking on HRV in a study population of 20 taxi drivers during a working day. In that study, HF-HRV tended to decrease within 5 min of cigarette smoking and recover within 15 min and these changes differed between daytime and nighttime (19). However, this study included only a small sample of smokers with no non-smokers, monitored only for 12 hours, and did not control for physical position in the statistical analysis. Here, we utilized Ecological Momentary Assessment (EMA) to sample multiple periods in the real-life environment, with concurrent ambulatory 24-hour ECG monitoring to determine the effect of cigarette smoking on HF-HRV.

MATERIALS AND METHODS

Study Design

This is a secondary analysis of data from a randomized, controlled intervention trial of cognitive-behavioral therapy (CBT) treatment of hostility (20). Data were collected between 2000 and 2005. Prior to randomization, we collected 24-hour ambulatory ECG recordings for all subjects; during this 24-hour period, subjects completed electronic diary entries, using a pre-programmed Palm Pilot personal digital assistant (PDA) time-synchronized with the ECG recording, which prompted diary entries approximately every 30 minutes throughout the period of 10:30AM-10:30PM. Diary entries provided EMA reports of physical position, medication use, caffeine consumption, alcohol consumption and cigarette smoking during waking hours. Participants were designated as either smokers or nonsmokers, based on their EMA responses during the 24-hour monitoring period, i.e., those who responded affirmatively to any prompt asking about smoking in the previous 30-minute period were designated as “smokers.” Within smokers, we compared HRV in the period following smoking to HRV following non-smoking periods. Between smokers and non-smokers, we compared mean HRV over the course of the day.

Study Participants

Eligibility and exclusion criteria have been previously described (20). Briefly, participants were recruited from the New York City area via print and radio advertisements to participate in a cognitive behavioral hostility and anger treatment study. Eligible participants were 20–45 years old, had a body mass index (BMI) ≥ 18.5 kg/m², and had no medical condition affecting the Autonomic Nervous System (ANS) or cardiovascular system, no affective disorder, no psychosis, no substance abuse, and were not currently taking any psychoactive medication. In addition, eligibility required scores more than one standard deviation above

the population normative means on the 50-point Cook Medley Hostility Scale (21) i.e., 26, and on the 30-point trait anger scale of the Spielberger State-Trait Anger Expression Inventory (STAXI) (22) i.e., 25.

Study Protocol

Prior to randomization, participants wore a Marquette 8500 Holter Electrocardiogram (ECG) recorder attached to two ECG leads (CM2 and CM5), used to record the ECG signal during daily living activities for 24 hours. During this period, participants were provided with a PDA used as an electronic diary for EMA sampling.

Measurement of Smoking Events

During the 24-hour ECG monitoring period, the participants completed 12 hours of EMA using a PDA programmed to prompt them to complete a survey every 30 ± 5 minutes between the hours of 10:30am and 10:30pm. The EMA survey questions used in this study are shown in Table 1' and included assessment of cigarettes smoked since last prompt (Yes or No) and description of current physical posture. Missed prompts were followed by a reminder 5 minutes after the original prompt, after which the device went silent until the next pre-scheduled prompt.

Measurements of Outcome Variables

The ambulatory ECG recording was evaluated using a Marquette 8000 ECG or MARS scanner, and then submitted to Marquette algorithms for initial QRS labeling and editing, resulting in an RR interval time series. Errors not detected by Marquette editing were corrected using editing algorithms developed at Columbia University (23, 24). The outcome variables were computed for the 5-minute epochs of RR intervals immediately preceding the PDA prompt, using Fourier transforms as described previously (25). The outcome variables, R-R interval (RRI), High Frequency Heart Rate Variability (HF-HRV) and the root mean square of successive differences in beat-to-beat RR intervals (RMSSD), were computed for each 5-minute epoch. Following the recommendation of van Roon et al. (26), we also analyzed a scale-free measure of HF-HRV, obtained by dividing HF-HRV by mean RRI^2 , that controls for the dependency of HRV on mean HR.

Statistical Analyses

A multilevel mixed model was estimated to generate maximum likelihood estimates of the difference in mean ln HF-HRV between smokers and non-smokers and the mean within-person change in ln HF-HRV when smoking (compared to when not smoking) among smokers, adjusting for potential person-level and momentary confounders. Secondary analyses used the same modeling approach to estimate the effects of smoking status (difference between smokers and non-smokers) and momentary smoking (current smoking versus not) on RMSSD and RRI for the 5-min epoch preceding the EMA report, as follows:

$$\begin{aligned} \text{Outcome}_{it} = & \alpha_i + \beta_1 \text{ Smoker}_i + \beta_2 \text{ Sex}_i + \beta_3 \text{ Age}_i + \beta_{4i} \text{ Momentary Smoking}_{it} + \\ & \beta_5 \text{ Momentary Position}_{it} + \beta_6 \text{ Momentary Alcohol Use}_{it} + \\ & \beta_7 \text{ Momentary Caffeine Use}_{it} + \beta_8 \text{ Momentary Medication Use}_{it} + \varepsilon_{it} \end{aligned}$$

where i indexes individuals and t indexes time.

The fact that parameters α and β_4 have subscripts “ i ” indicates that these are treated as random effects; i.e., the model allows for the intercept and the momentary effect of smoking on the outcome to be different for each individual. The Momentary Smoking measure was person-centered so that the coefficient of smoking status, β_1 , equals the difference between smokers (averaged over occasions when they smoked and when they did not) and non-smokers on the outcome, adjusting for covariates. The mean level of β_{4i} provides an estimate of the average (across persons) momentary effect of smoking.

The within-person error term, ϵ_{it} , allowed for unmeasured autocorrelation in the outcome, fitting a quasi-simplex error structure (27) taking into account the non-constant time intervals between assessments. Specifically, the error structure is made up of two components, one conforming to a first-order serial autocorrelation structure with varying time intervals between observations and the other exhibiting no autocorrelation; the latter could be interpreted as “measurement error”, consistent with the “error” component of Kenny and Zautra’s (28) trait-state-error model. (The trait component is captured by the α_i).

For all estimated parameters, a p -value less than .05 was considered to be statistically significant. All analyses were performed using mixed modeling software (SAS 9.3, Proc Mixed).

This analytic approach was described in detail in (29).

Institutional Review

This study, as well as the original study protocol, was approved by the Institutional Review Board (IRB) of Columbia University Medical Center. All participants provided informed consent prior to participating in the study.

RESULTS

Demographics

35 smokers and 114 non-smokers provided EMA and HRV data for 5067 periods. The sample ($N=149$) was 47% male, and the average standard deviation (SD) age and BMI were 30.8 (6.8) years and 23.7 (3.7) kg/m^2 . Table 2 shows the baseline demographics by smoking status in the sample. The majority of smokers were male while the majority of non-smokers were female ($p=0.02$ by Fisher’s exact test). Neither age nor body mass index differed significantly by smoking status.

RR Interval and HRV in smokers during smoking and non-smoking periods

Among the 35 smokers, there were 259 episodes of smoking during the monitoring days. Within smokers, there were significant effects of smoking on RRI and HF-HRV: RRI following a smoking event was lower than for non-smoking periods (711.4 vs 740.8 msec, difference = -29.4 ms ($p<0.001$)), and ln HF-HRV was reduced after smoking when compared to periods of not smoking (5.09 vs 5.40, difference = -0.31 ms^2 ($p=0.04$)). The scale-free measure of HF-HRV, computed to control for the dependency of HRV on mean

HR (28), also was reduced after smoking, difference = -0.24 ($p=0.06$). The effect of smoking on RMSSD was marginally significant ($p=0.06$). The within-person effects of cigarette smoking on HRV and RRI are shown in Table 3.

HRV in smokers vs non-smokers over 24 hours

Averaged across all periods, mean RRI $\pm$ SD was 725.85 ± 13.17 ms for smokers and 768.88 ± 7.18 ms for non-smokers, a statistically significant difference ($p=0.005$). Similarly, HF-HRV $\pm$ SD was 5.24 ± 0.14 ln ms^2 for smokers and 5.63 ± 0.07 ln ms^2 for non-smokers ($p=0.02$). The scale-free measure of HF-HRV was marginally lower in smokers than in non-smokers, -7.88 for smokers and -7.63 for nonsmokers ($p=0.07$). RMSSD $\pm$ SD was marginally lower in smokers than in non-smokers, 33.92 ± 2.69 ms^2 for smokers and 39.44 ± 1.47 ms^2 for non-smokers ($p=0.08$). The cross-sectional comparison between smokers and non-smokers is shown in Table 4.

DISCUSSION

We found that among smokers, smoking episodes during daily living were associated with a reduced HF-HRV compared to non-smoking episodes, supporting our hypothesis that smoking is associated with reduced cardiac vagal regulation on a moment-to-moment basis. The within-person effect of cigarette smoking on RMSSD achieved marginal significance ($p < .06$). Correspondingly, between-person comparisons revealed reduced average HF-HRV among smokers (pooled across periods of smoking and non-smoking) when compared to the non-smokers, averaged across all periods, as predicted. This finding supports our prediction that HF-HRV is lower among smokers when compared to non-smokers. RMSSD among smokers, averaged across all periods, was marginally lower when compared to non-smokers. Adjusting for mean RRI marginally attenuated these findings.

The findings of this study suggest that HF-HRV, a frequency domain measure and an index of cardiac vagal regulation, was reduced within the smokers, when smoking during daily living. This is consistent with previous literature indicating that both frequency and time domain measures of HRV are reduced among smokers when compared to non-smokers (10, 11, 30). Both the results obtained from the within-person analysis of cigarette smoking and from the cross-sectional comparison between smokers and non-smokers participating in this study are consistent with previous studies showing that acute and chronic smoking are associated with reduced HRV (10, 17, 18).

There are, however, some possible inconsistencies between our findings and those of Hayano et al. and Kobayashi et al. (10, 19). Both of these studies found that cigarette smoking caused an acute reduction in HF-HRV at 3–5 min after smoking, with HF power returning to baseline by 10 min. Our diary asked only whether participants had smoked within the last 30 min. Therefore, we cannot determine precisely when within this 30 min window the cigarette smoking occurred and what the time course of recovery was. Moreover, other methodological differences make these comparisons difficult. Hayano et al. rigorously controlled exposure to cigarette smoking in a laboratory setting, with subjects smoking 4 cm of a cigarette containing 1.0 mg of nicotine over a 2 min period while in the supine position. In contrast, as field studies we and Kobayashi et al. allowed subjects to

smoke ad libitum, smoking as frequently and as completely as they chose while in the seated position.

While there are multiple components of cigarette smoke, it is likely that the effects on cardiovascular autonomic regulation involve nicotine. For example, a 4 mg dose of oral nicotine reduces HF-HRV in non-smokers, indicating that nicotine itself leads to reduced vagal regulation (31). Environmental exposure to nicotine, measured in a commercial airport, was also associated with reduced HF-HRV (32).

Cigarette smoke stimulates the release of catecholamines through effects on nicotinic cholinergic receptors in peripheral postganglionic sympathetic nerve-endings and the adrenal medulla (33). This nicotine-induced release of catecholamines is associated with both acute and chronic cardiovascular events like cardiac rhythm disorders (5, 18). A previous animal study showed that the perfusion of nicotine to the sinoatrial node in dogs leads to both a cholinergically-mediated slowing of the heart and a non-reaction of the heart to electrical stimulation of the cervical vagus for >5 minutes. This non-reaction of the heart to vagal stimulation corresponds to the ganglionic blocking effect of nicotine, also manifested by cigarette smoking in humans (34).

The fine particular matter of the size 2.5 microns (PM2.5) are particles that have a size to reach deep into the respiratory tract and are therefore often measured by health authorities as an index of general air-pollution. Liao et al. invited 26 volunteer elderly to a 21-day study of ECG monitoring and continuous measurement of PM2.5. They found that lower autonomic control was significantly associated with higher levels of PM2.5 indoors as well as outdoors (35). Since PM2.5 is also a component of tobacco smoke, in addition to the nicotine pathway, this may be a mechanism for the vagal down-regulation we have found in smokers.

Our findings may contribute to an understanding of the interrelationships of hostility and smoking in the pathogenesis of coronary artery disease. There is substantial evidence that cigarette smoking and reduced HRV are, both separately and in combination, associated with an increased risk for developing cardiac disease (1, 36). A recent meta-analysis concluded that hostile behavior is associated with increased coronary heart disease (CHD) events both in healthy populations and in populations with already diagnosed CHD (37). However, the authors found that the harmful effects of hostility on CHD were no longer significant in either population after adjusting for smoking. Nonetheless, Wong et al. studied the possible mechanisms responsible for the association between hostility and cardiovascular events in a large sample of patients with CHD. The authors concluded that a large part of the association is attributed to specific poor health behaviors like physical inactivity and smoking (38). We have previously demonstrated that hostility is inversely related to parasympathetic cardiac control, reflected by reduced HF-HRV in a young, healthy population. That finding and the findings of this study may suggest that altered autonomic regulation could be a pathogenic mechanism linking high hostility levels and a higher risk of developing coronary artery disease (CAD) (39). We are not aware of any previous studies looking at the within-person effect of cigarette smoking on HF-HRV within a hostile population. Our findings suggest that smoking events further depress parasympathetic

cardiovascular regulation in hostile individuals, which may transiently heighten their vulnerability to acute cardiac events.

Strengths

A strength of this study is the collection of multiple ecologically-valid date/time-stamped diary entries that enabled within-person analyses. Diary entries of smoking assessed in real time decrease the likelihood of error in participants' recollections of smoking frequency. Additionally, continuous ECG recording allowed HF-HRV to be quantified for specific periods just prior to each EMA report. The use of PDAs reduced the risk of data loss.

Limitations

This study was limited by its relatively small sample size of 149 participants (35 smokers and 114 non-smokers). Individuals with high hostility levels were selected, which may limit generalizability of the findings. Further application of this data collection and analytic approach to larger, normative samples could yield further insight into the effects of smoking on HRV in everyday life. Finally, there was substantial dropout in the study.

CONCLUSION

Both the within-person effect of cigarette smoking and the effect of smoking status are associated with reduced HF-HRV. They suggest that cardiac vagal regulation is lowered by cigarette smoking, which may be one of the many pathophysiological effects by which smoking increases cardiovascular risk. This study demonstrates that HF-HRV is transiently decreased after each episode of smoking in daily life with EMA. This strongly suggests that each and every cigarette smoked is a transient risk factor for untoward events related to transiently lowered parasympathetic cardiac effects. Future studies should examine whether these HRV changes mediate the effect of cigarette smoking on the risk of harmful cardiovascular events.

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List of abbreviations

HRV	Heart Rate Variability
HF	High Frequency
LF	Low Frequency
RRI	R-R interval
RMSSD	Root mean square of successive differences in RR intervals
SD	Standard Deviation

EMA	Ecological Momentary Assessment
BMI	Body Mass Index
ECG	Electrocardiogram
CVD	Cardiovascular Disease
CHF	Congestive Heart Failure
CBT	Cognitive-behavioral Therapy
PDA	Personal Digital Assistant
ANS	Autonomic Nervous System
STAXI	State-Trait Anger Expression Inventory
SAS	Statistical Analysis System
IRB	Institutional Review Board
PM 2.5	Particular matter of the size 2.5 microns
CHD	Coronary Heart Disease
CAD	Coronary Artery Disease

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TABLE 1

EMA Survey Questions Used in the Study

ATTRIBUTE	Range min	Range max	Question text	Name of values (min to max)
POSITION	1	3	Right now I am:	Sitting=1, Standing=2, Reclining/Laying Down=3
CAFFEINE	No	Yes	Since the last beep I had caffeine?	
SMOKING	No	Yes	Since the last beep I had tobacco?	
ALCOHOL	No	Yes	Since the last beep I had alcohol?	
MEDICATION	No	Yes	Since the last beep I had medication?	

TABLE 2

Baseline Demographics by Smoking Status in the Study Population (N=149)

	Smokers	Non-Smokers
<i>N</i>	35	114
Age (years), mean ($\pm$ SD)	29.0 $\pm$ 7.4	31.4 $\pm$ 6.5
Sex (M/F) (%)	66/34	42/58
BMI (kg/m ²), mean ($\pm$ SD)	23.8 $\pm$ 3.9	23.7 $\pm$ 3.6
Race/Ethnicity, N (%)		
American Indian	1 (2.8%)	0
Asian/Pacific Islander	0	14 (12.3%)
Black, not Hispanic	9 (25.7%)	19 (16.7%)
Hispanic	11 (31.5%)	23 (20.2%)
White, not Hispanic	14 (40%)	55 (48.2%)
Other or unknown	0	3 (2.6%)
STAI, mean ($\pm$ SD)	30.9 $\pm$ 3.7	31.0 $\pm$ 4.36
CKM, mean ($\pm$ SD)	33.4 $\pm$ 5.4	32.6 $\pm$ 5.6

N=Number of participants. SD=Standard Deviation. M=Male. F=Female. BMI=Body Mass Index. STAI = Spielberger Trait Anxiety Inventory Total Score. CKM = Cook-Medley Hostility Scale Total Score

TABLE 3

Within-person Effect of Cigarette Smoking on HRV and R-R Interval

Outcome variables	β smoking	95% CI	P-value
RRI (ms)	-29.38	-41.37 to -17.39	< 0.001
ln HF-HRV (ln ms ²)	-0.31	-0.60 to -0.02	0.04
Ln HF-HRV scaled to mean RRI	-0.24	-0.49 to 0.01	0.06
RMSSD (ms)	-2.04	-4.17 to 0.08	0.06

The estimates listed here come from a mixed model that statistically controls for (physical position, medication use, caffeine consumption, alcohol consumption and cigarette smoking) during waking hours. β smoking= Unstandardized regression coefficient estimating, for smokers, the difference in HRV between periods when they smoked and periods when they did not. CI=Confidence Interval. RRI=R-R interval. Ln HF-HRV=Natural Logarithm High Frequency Heart Rate Variability. RMSSD= The root mean square of successive differences in beat-to-beat R-R interval. ms= milliseconds. ms²=milliseconds²

* Following the recommendation of van Roon et al. (26) we also analyzed a scale-free measure of HF-HRV, obtained by dividing HF-HRV by mean RRI², that controls for the dependency of HRV on mean RRI.

TABLE 4

Adjusted Mean Levels of HRV and RR Interval for Smokers and Nonsmokers

Outcome variables	$\bar{X}_{\text{non-smoker}}$	$\bar{X}_{\text{smoker}}$	P-value
RRI (ms) $\pm$ SD	768.88 $\pm$ 7.18	725.85 $\pm$ 13.17	0.005
ln HF-HRV (ms ²) $\pm$ SD	5.63 $\pm$ 0.07	5.24 $\pm$ 0.14	0.01
Ln HF-HRV scaled to mean RRI	-7.63	-7.88	0.07
RMSSD (ms) $\pm$ SD	39.44 $\pm$ 1.47	33.92 $\pm$ 2.69	0.08

This table shows the least square means for the Nonsmoker and the Smoker group and the p-value represents the difference between these two groups. The estimates listed here come from a mixed model that statistically controls for (physical position, medication use, caffeine consumption, alcohol consumption and cigarette smoking) during waking hours. $\bar{X}_{\text{non-smoker}}$ = Mean Population of non-smokers. $\bar{X}_{\text{smoker}}$ = Mean Population of smokers. RRI=R-R Interval. Ln HF-HRV=Natural Logarithm High Frequency Heart Rate Variability. RMSSD= The root mean square of successive differences in beat-to-beat R-R interval. ms= milliseconds. ms²=milliseconds². SD= Standard Deviation.