Original Article

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Arterial Compliance and Autonomic Functions in Adult Male Smokers

Physiology Section

SUKHMANI SAINI[1], YOGESH SAXENA[2], RANI GUPTA[3]

ABSTRACT

Introduction: Smoking is known to augment sympathetic activity and may lead to increased arterial stiffness. Several studies have reported association of increased sympathetic activity and arterial stiffness to cardiovascular risks among smokers. Pulse Wave Velocity (PWV) of peripheral arteries, instead of aorta can be used as a non-invasive indicator of arterial stiffness.

Aim: To measure non-invasively, the autonomic functions and peripheral arterial stiffness in smokers, and to find out whether the aforementioned factors are modified by the level of physical activity in these smokers.

Materials and Methods: This cross-sectional analytical study was conducted in the Department of Physiology, HIMS, Dehradun, over a period of 12 months (2013-2014) on 100 adult males (20-40 years); 50 smokers and 50 non-smokers. The parameters analysed include relevant anthropometric and cardiovascular parameters, Pulse Wave Velocity (PWV), sustained Hand Grip Test (HGT) and Heart Rate Variability (HRV) domains. Data interpretation and analysis was carried out using SPSS 17.0. Comparison of the above mentioned parameters amongst groups was done with unpaired t-test. The relationship of pack-years & physical activity with vascular functions was assessed by Pearson's correlation. Interaction of various grades of smoking and physical activity with Cardiovascular System (CVS) parameters was assessed by one-way ANOVA.

Results: Smokers had higher values of PWV (5.7±0.5m/s) as compared to non-smokers (4.8±0.4m/s) ($p<0.001$). ΔDBP during HGT was lower (7±3.18mmHg) among smokers as compared to non-smokers (19.4±3.5mmHg) ($p<0.001$). Smoking (pack-years) was positively related to PWV ($r= .03$) but showed a weak negative relationship with change in Diastolic Blood Pressure (ΔDBP) ($r= -0.084$, $p=0.56$) showing that, more the frequency of smoking, the more was arterial stiffening and the lesser was the sympathetic response to the HGT. The smokers had significantly higher sympathetic activity; Low Frequency (LF) & Low Frequency: High Frequency ratio (LF: HF) ($p<.001$) whereas High Frequency (HF) was significantly lower ($p<.001$) showing a decline in parasympathetic activity.

Conclusion: Smokers demonstrated higher peripheral PWV and higher intrinsic sympathetic activity and this increase in intrinsic sympathetic activity may lead to increased arterial stiffness. Interaction of autonomic function and PWV with levels of physical activity and grades of smoking showed no significant differences, suggesting the fact that increased physical activity or reduced smoking may not have any effect on the endothelial dysfunction or CVS morbidity caused by smoking.

Keywords: Arterial stiffness, Pulse wave velocity, Sympathetic dysfunction

INTRODUCTION

Smoking is a major and independent risk factor for cardiovascular morbidity and mortality. The tobacco epidemic kills nearly 6 million people each year, of which 5 million are users or ex users of tobacco and others are non-smokers who die from exposure to second-hand smoke [1]. Scientific evidences confirm that smokers face significantly increased risk of harm to the heart and blood vessels [2]. Furthermore, any amount of smoking, even light or occasional, damages the heart and blood vessels [3]. Smoking even one cigarette has been reported to cause changes in vascular endothelium [4]. Smoking has been shown to affect arterial elastic properties unfavourably [5]. Vascular dysfunction is the key process involved in the development of cardiovascular diseases. Smoking causes endothelial damage [6] and autonomic dysfunction, which can be used both as diagnostic and prognostic indicators of cardio-vascular diseases in smokers [7].

AIM

The current study is being done to test the hypothesis that smokers have increased arterial stiffness and autonomic dysfunction irrespective of the grade of smoking or level of physical activity.

MATERIALS AND METHODS

This cross-sectional analytical study was conducted in the Department of Physiology, Himalayan Institute of Medical Sciences (HIMS), Swami Ram Nagar, Dehradun, over a period of twelve months (2013-2014) on 100 adult males (20-40 years); 50 smokers and non-smokers each after taking clearance from the institutional ethical committee. Sample size was determined using the formula for comparing the difference of means between the groups [8] with $\alpha=0.05$, $\beta=90\%$, which gave a sample size of $n=40$ for each group, which was later extended to 50, to make up for non-compliance and aberrant values. The 100 selected male volunteers (20-40 years) were divided into two groups: Non-smokers ($n = 50$); normal healthy adults who had never smoked and smokers ($n=50$); clinically healthy smokers with history of smoking for at least six months or more. Exclusion criteria included past history of stroke, diabetes, hypertension, angina, atherosclerosis, established Buerger's disease. Volunteers were asked to report in the department in the morning between 9am and 10am, preferably without heavy meals and well rested on the preceding night. They were familiarized with the procedure of all the tests. Data related to anthropometric parameters, relevant medical history and smoking history was collected at the point of entry using data recording questionnaire. Physical Activity assessment was done using International Physical Activity Questionnaire (IPAQ) with 7 days recall [9]. Volunteers were instructed to avoid nicotine, caffeine and any kind of physical exercise in the preceding 24 hours. Recording was done at an ambient temperature of 25°C. Following a rest of 15 minutes, recording of ECG and PWV was done for 5 minutes

using windows based computerized polygraph i.e. Physiopac (PP-8-Medicaid systems; 8 channels (7 universal and 1 exclusively for spO_2). ECG was recorded using German silver plated surface electrodes held in position by electric straps and electrolyte jelly was employed as an interface between the electrode and the source during the event. Heart Rate Variability (HRV) parameters were derived from the recordings [10]. Simultaneous recording of PWV was done by using a digital photoplethysmograph wrapped on the tip of the left index finger with the help of an inbuilt Velcro strap connected to the same Physiopac. Time interval between R wave and onset of pulse wave form was calculated by the polygraph machine. Distance was then measured from sternal notch to the tip of the left index finger. PWV was calculated by dividing this distance by the time interval between R wave and onset of pulse wave form. Handgrip Dynamometer (model number PP-105- by INCO Ambala) was used for the sustained Handgrip Test (HGT). Baseline BP and HR were recorded in sitting position. The subject then held the device in the non-dominant hand, with the arm dangling beside. Maximum Voluntary Contraction (MVC) was recorded prior to the test by asking the subject to press the device with maximum force, and maintain it for five seconds without moving any other part of his body. The subject was then asked to press and maintain the dynamometer at 30% of MVC for 3 minutes. The rise in the BP just before the release of the grip was taken as the index of response to the test. Change in Diastolic Blood Pressure (ΔDBP) i.e. difference between baseline DBP and diastolic BP just before release was used to grade the result as normal (>16mmHg); borderline (11-15 mmHg) and abnormal (<10 mmHg) [11]. Double product (DP), i.e., SBP x Heart Rate, was calculated to assess the myocardial oxygen demand [12].

RESULTS

The study carried out on the 100 subjects found significantly higher LF:HF ratio in smokers vs. non-smokers(p<0.001) [Table/Fig-1]. This finding was also supported by the observation that on performing HGT smokers had a lower ΔDBP as compared to non-smokers (p<0.001) [Table/Fig-1]. Interaction was studied among autonomic functions and PWV with the level of physical activity and grades of smoking but no significant differences were found. Our findings are as follows:

S. No.	Parameters	MEAN ± SD		'p'-value
		Controls (n=50)	Cases (n=50)	
1.	Age (years)	29.3±6.9	31.7±6.4	0.08
2.	Height (cm)	166.8±8.5	166.4±7	0.81
3.	Weight (Kg)	66.3±8.3	65.1±9.9	0.51
4.	BMI (Kg/m^2)	23.8±2.0	23.4±2.7	0.40
5.	Resting Heart rate (bpm)	73.7±4	74.0±4.5	0.764
6.	Resting SBP (mmHg)	113.5±10	117.9±10.1	0.03*
7.	Resting DBP (mmHg)	76±5.9	81.2±4.6	0.02*
8.	Resting Double Product (mmHg per min)	8387±972.3	8749±1067.7	0.08
11.	SBP just before release	130.7±8.6	133.6±5.9	0.05
12.	DBP just before the release	95.4±4.3	88.2±3.9	0.00**
13.	Change in DBP(ΔDBP)	19.4±3.5	7.0± 3.3	0.00**
14.	Low Frequency (LF) (nu)	58.5±13.1	73.8±10	0.00**
15.	High Frequency (HF) (nu)	38.0±12.4	21.2±7.0	0.00**
16.	LF/HF Ratio	1.82±1.04	3.93±1.6	0.00**
19.	Pulse wave Velocity(PWV) (m/s)	4.8±0.44	5.797±0.55	0.00**
20.	Resting Double Product(DP) (mmHg per min)	8387±972.3	8749±1067.7	0.08

[Table/Fig-1]: Comparison of demographic, anthropometric, CVS parameters, autonomic response to HGT, autonomic balance (HRV), pulse wave velocity (PWV) & resting DP between the controls and the cases.
Values in Mean±SD, *Significant (p< 0.05) **Highly significant (p< 0.001) Unpaired t test.

[Table/Fig-1] shows the comparison of the demographic, anthropometric, CVS, HGT, HRV, PWV and resting DP parameters between the controls and the cases. On comparison, there was no statistically significant difference in the demographic & anthropometric characteristics between the controls and the cases. On comparison of CVS parameters, Resting SBP and DBP were both significantly higher in cases than in controls (p=0.03 and p=0.02 respectively) but heart rate although higher among the cases was statistically non-significant. The comparison of autonomic response to sustained HGT among the two groups found that cases had average SBP 'just before release' of 133.6±5.9 mmHg; DBP 'just before the release' of 88.2±7.9 mmHg and 'the change in' DBP, Δ of 7±3.18 mmHg respectively. The average increase in DBP among cases was found to be abnormal, whereas it was normal in the control group. On comparison, there were statistically significant lower values of resting SBP (p=0.03) among the controls. DBP 'just before the release' and Δ DBP were significantly lower among the cases (p<0.001). On comparison of HRV parameters, we found that the controls had an average LF value of 58.5±13.1 nu; HF of 38.0±12.4 nu and LF/HF ratio of 1.82±1.04. The cases were found to have average LF value of 73.8±10 nu; HF of 21.2±7.0 nu and LF/HF ratio of 3.93±1.6. On comparison, the controls had significantly lower values of HF and LF/HF ratio (p<0.001). Whereas, the cases had significantly higher values of LF (p<0.001). Comparison of the PWV, LF/HF ratio, ΔDBP & resting DP between controls & cases found highly significant higher value of ΔDBP among controls(19.4±3.5; p=0.00) [Table/Fig-1]. To further corroborate this finding, controls had significantly lower value of LF/HF ratio and PWV than the cases. Resting DP, which is an indicator of myocardial oxygen demand, was also higher among the cases as compared to the controls, although statistically insignificant.

[Table/Fig-2] shows the comparison of the pulse wave velocity, LF/HF ratio, ΔDBP and DP between the smokers having low and moderate physical activity levels with various grades of smoking. There was no statistically significant difference in cardiovascular parameters, namely ΔDBP, LF/HF ratio, PWV and resting DP among different levels of physical activity & gradings of smoking in both the controls & the cases.

[Table/Fig-3] shows the correlation between anthropometric variables, PWV, autonomic functions variables and pack-years score among the cases. Among the anthropometric variables, there was highly significant positive correlation between weight with height and BMI. Resting DP was shown to be significantly positively correlated with age & BMI of the cases. However, resting DP was found to have statistically insignificant but negative correlation with PWV, LF/HF ratio and ΔDBP, and positive correlation with PY. Among the autonomic function variables, there was statistically non-significant but positive correlation between PWV and LF/HF. Also there was non-significant negative correlation between LF/HF and ΔDBP. Pack-years showed a non-significant positive correlation with pulse wave velocity & LF/HF; and negative correlation with Δ DBP.

DISCUSSION

Smoking is a major health concern throughout the world, with increasing numbers of smokers added each year. In India alone there are 182 million smokers out of the global tobacco users of about 930 million [13]. Smoking is a major and independent risk factor for cardiovascular morbidity and mortality. It is associated with autonomic dysfunction. It has also been reported to augment sympathetic nervous system activity [7]. It is also a well-known risk factor of vascular endothelium damage and hence vascular dysfunction [6]. PWF is a marker for arterial stiffness and vascular dysfunction which seems to be the key process involved in the development of cardiovascular disease. Vascular dysfunction can

Characteristics of the Cases (n=50)									
Grading of smoking	Light			Moderate			Heavy		
Level of Physical Activity	Low (n=16)	Moderate (n=10)	p-value	Low (n=6)	Moderate (n=8)	p-value	Low (n=6)	Moderate (n=4)	p-value
Parameters									
Change in DBP (mmHg)	6.9±1.51	5.8±1.36	.054	5.67±1.51	5.82±1.4	.456	5.33±2.65	5.17±2.52	.634
LF/HF Ratio	4.25±1.238	3.20±1.476	.062	3.83±2.137	3.75±1.488	.933	4.17±1.835	4.25±2.062	.948
Pulse wave Velocity (m/s)	5.94±.680	5.70±.483	.347	5.67±.516	6.00±.535	.264	5.83±.408	6.00±.816	.676
Double Product (mmHg per min)	8499.50 ± 794.074	9028.00 ± 1460.934	.313	9130.00 ± 774.364	8620.00 ± 1118.622	.359	8456.00 ± 828.840	9176.00 ± 1631.150	.378

[Table/Fig-2]: Comparison of pulse wave velocity (PWV), LF/HF ratio, Change in DBP & resting DP between low & moderate physically active cases with various grades of smoking (n=50).
Values in Mean±SD *Significant (p< 0.05) **Highly significant (p< 0.001) Unpaired t test.

Parameter	Age	Weight	Height	BMI	DP	PWV	LF/HF	ΔDBP	PY
Age	-	r = -.025, p=.863	r = -.182, p=.207	r = .075, p =.605	r =286* p =.044	r = -.106 p =.462	r = -.095, p =.510	r = -.022, p =.879	r = .543**, p =0.00
Weight	-	-	r = .670** p =0.00	r = .835** p =0.00	r = .231, p =.106	r = .060, p =.680	r = -.048, p =.740	r = .140, p =.332	r = .170, p =.238
Height	-	-	-	r = .162 p =.260	r = .087 p =.548	r = .122, p =.398	r = -.111, p =.444	r = .196, p =.173	r = .000, p =1.00
BMI	-	-	-	-	r = .350* p = .013	r = .007, p =.964	r = .024, p =.868	r = -.002, p =.989	r = .217, p =.131
DP					-	r = .096, p = .506	r = -.139 p = .337	r = -.076 p = .602	r = .035 p = .811
PWV	-	-	-	-		-	r = .007, p =.962	r = .227, p =.112	r = .030, p =.838
LF/HF	-	-	-	-		-	-	r = -.104, p =.472	r = .135, p =.351
ΔDBP	-	-	-	-		-	-	-	r = -.084, p =.561

[Table/Fig-3]: Correlation between anthropometric variables, resting DP, pulse wave velocity, autonomic functions variables and pack-years score among the cases
Values in Mean±SD *Significant (p< 0.05) **Highly significant (p< 0.001) Unpaired t test.

be assessed clinically by pulse wave velocity. Smoking is known to cause increase in pulse wave velocity [14].

In the present study, when demographic & anthropometric characteristics, namely, age, height, weight and BMI, between the smokers and the non-smokers were examined [Table/Fig-1], there was no significant difference noted. These might have had minimal effect on the variables being studied. There were statistically significant higher values of resting SBP& DBP among the smokers, who also had higher values of resting heart rate and Double Product (DP), although these differences were statistically insignificant as compared to non-smokers.

On analysing the BP and heart rate findings of our study [Table/Fig-1] Resting SBP and DBP were both significantly higher in cases than in controls (p=0.03 and p=0.02 respectively) but heart rate although higher among the cases was statistically non-significant. These findings were supported by Chevalier RB et al., who reported that smokers had a faster resting heart rate than non-smokers [15]. He J et al., too, noted that even passive smoking was associated with significant rise not only in heart rate but also in blood pressure [16]. The acute rise in blood pressure was found to be associated with smoking by many other researchers like Omvik P and Green MS et al., [17,18]. The HGT is considered to be a specific, sensitive, reproducible, simple and non-invasive test of sympathetic function [19]. The change in Diastolic Blood Pressure (ΔDBP) is the most sensitive and specific measurement in diagnosing dysautonomic conditions [19]. Smoking is known to lead to widespread augmentation of the sympathetic nervous system activity [7]. When sympathetic activity response to the sustained hand grip test (HGT) was examined, we noted significantly lower values of maximum DBP 'during sustained handgrip' and 'change in' DBP, i.e. ΔDBP among the smokers [Table/Fig-1]. However, there was no significant difference in the ΔDBP value when the two groups were compared on the basis of grades of smoking and levels of physical activity. The aforementioned findings of our study were supported by a cross sectional study by Tayade MC et al., who also reported significantly lower change in DBP among smokers on the sustained handgrip test [20] indicating a decrease in the sympathetic response. This finding was also in accordance with the findings of MerviKotamäki who reported a significantly lower change in DBP among smokers in the sustained handgrip test in a study conducted among military pilot candidates [21].

The sympathetic activation induced by smoking, depends on an increased release and/or a reduced clearance of the catecholamines [20]. Plasma renin levels& plasma noradrenaline levels in response to sustained hand-grip test were found to be significantly higher in smokers, in a study done by MerviKotamäki [21], further supporting the fact that smoking causes increased sympathetic activity. The impairment of baro-reflex sensitivity caused by smoking further worsens the condition, due to the inability to counteract the sympathetic activation [22]. Also, down regulation of beta adrenergic receptors has also been shown in long term smokers [20]. So these findings probably further corroborate our findings that smokers had a significantly lower (ΔDBP), the index of sympathetic response to sustained handgrip test.

When Heart Rate Variability (HRV) parameters were compared between the smokers & the non-smokers [Table/Fig-1], the smokers were found to have significantly higher values of Low Frequency normalized units (LFnu) and LF/HF ratio, indicating shift of sympathovagal balance towards sympathetic activity. They, however, had significantly lower values of High Frequency normalized units (HFnu). Our findings were strongly supported by a study conducted by Barutcu I et al., who also reported that LF/HF ratio was significantly higher in smokers than in non-smokers [23]. In addition, in another study, Hayano J et al., reported lower HF(nu) of HRV in smokers [24]. Our findings were also similar to those noted by Tsuji H et al., Thayer JF et al., and Kupari M et

al., [25-27]. Further, Kobayashi F et al., also reported that LF/HF ratio increased within 5 min after smoking, further supporting our finding that it is cigarette smoke which is responsible for shifting the sympathovagal balance towards sympathetic activity [28]. In addition to this, higher LF/HF ratio with smoking was also reported by Minami J et al., and Alyan O et al., [29,30]. Cagirci G et al., also reported that smoking was associated with significantly higher values of LF(nu) and LF/HF ratio, and significantly lower value of HF(nu), concluding the adverse effect of smoking on autonomic function, & hence the increased risk for cardiovascular events [31].

Double Product is a valid estimation of oxygen consumption by the heart [32]. The higher values of Double Product in smokers in our study [Table/Fig-1] were supported by Singh K et al., who reported higher values of DP among smokers as compared to non-smokers [33]. Similar findings were also noted by Papathanasiou G et al., and Czernin J et al., [34,35]. DP was also found to be persistently and markedly increased among heavy smokers. This could probably be the result of higher workload on the heart of smokers, resulting in higher myocardial oxygen demand [36].

Pulse wave velocity, an indicator of arterial stiffness [37], when compared among the two groups [Table/Fig-1] was significantly higher among the smokers. However, when the interaction between level of physical activity and grade of smoking was studied, we found no significant difference in the pulse wave velocity of light smokers (p=0.34), moderate smokers (p=0.26) or heavy smokers (p=0.67), at various levels of physical activity. This probably indicated that there may be no effect of physical activity levels or grades of smoking on PWV. Our findings of increased PWV are supported by the following literature. Kim JW et al., in a study reported that smoking causes increase in brachial pulse wave velocity [14]. In another study, Binder S et al., also reported higher PWV among smokers [37]. Similar finding of higher pulse wave velocity were also noted by Kubozono T et al., Levenson J et al., and Jatoi NA et al., [38-40]. Interestingly, Brunel P et al., found an increase in PWV after acute smoking [41], supporting our finding that it is in fact, cigarette smoke, which results in higher PWV among study subjects. This finding, further stands corroborated by a study conducted Mahmud and Feely, who reported an increase in pulse wave velocity even after smoking a single cigarette in chronic smokers [42]. Smoking is known to be associated with endothelial damage [6] which results in increased arterial stiffness [14] and reduced arterial compliance. These factors are emerging as important risk factors for cardiovascular diseases. They can easily be assessed clinically by newer non-invasive methods, making them suitable for bed side studies in clinical settings. Arterial stiffness can thus be used as a measure of endothelial function [43] and an independent predictor of cardiovascular death [44].

Thus, on the basis of our results we may suggest that smoking causes increased arterial stiffness and autonomic dysfunction in smokers, which can be measured non-invasively and both these factors possibly remain unaltered by the grade of smoking or the level of physical activity. Further studies may be required to throw light on such phenomena and establish whether giving up smoking altogether may benefit smokers by reversing these adverse effects.

LIMITATION

Levels of nicotine and oxidative free radicals in the blood of the subjects were not quantified due to limited resources. Other methods of recording PWV are available but were not used due to invasive nature. The sample size of 100 subjects may be too less and larger studies are required.

CONCLUSION

To conclude, an increased sympathetic activity among smoking group was evident by an increased low frequency normalized unit (LFnu) and LF:HF ratio as compared to non-smokers This was further substantiated by lesser rise in DBP (ΔDBP). High frequency normalized unit (HFnu) of smoking group was significantly lower in smokers indicating increased sympathetic & decreased parasympathetic activity. Also, interaction studied among autonomic functions and PWV with the level of physical activity and grades of smoking found no significant difference between the two groups, indicating that the arterial stiffness & autonomic dysfunction caused by smoking is not dependent on the grade of smoking or physical activity levels per se.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Physiology, Himalayan Institute of Medical Sciences, SRHU, Dehradun, India.
2. Associate Professor, Department of Physiology, Himalayan Institute of Medical Sciences, SRHU, Dehradun, India.
3. Professor and Head of Department, Department of Physiology, Himalayan Institute of Medical Sciences, SRHU, Dehradun, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sukhmani Saini,
Subhartipuram, Kotda Santaur, Aamwala Road, P.O Chandanwadi
Nanda ki Chowki, Prem Nagar, Dehradun-248007, India.
E-mail: sukhmanisaini@outlook.com

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