

Acute and Chronic Effect of Cigarette on Right and Left Ventricular Diastolic Function

Seyed Masoud Seyedian,¹ Shahla Majididi,¹ Lida Asgharinejad,¹ Mehrnoush Esmaeili,² Farzaneh Ahmadi,^{1*} and Molook Salehzadeh³

¹Department of Cardiology, Atherosclerosis Research Center (Cardiovascular Disease Center), Faculty of Cardiology, Jundishapur University of Medical Sciences, Ahvaz, IR Iran

²Department of Cardiology, Faculty of Cardiology, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

³Golestan Hospital, Clinical Research Development Unit, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, IR Iran

*Corresponding author: Farzaneh Ahmadi, Department of Cardiology, Atherosclerosis Research Center (Cardiovascular Disease Center), Faculty of Cardiology, Jundishapur University of Medical Sciences, P. O. Box: 61355-173, Ahvaz, IR Iran. Tel: +98-9161113490; +98-6113743092, E-mail: asgharinejadlida@yahoo.com; ahmadithc@yahoo.com

Received: December 7, 2014; Revised: May 19, 2015; Accepted: May 25, 2015

Background: One billion people in the world are addicted to cigarettes; due to smoking and related illnesses, over five million people in the world, suffered death yearly. Epidemiological studies have shown that more than one case out of 10 cases of cardiovascular deaths, which include 54% of all deaths worldwide, is due to cigarettes.

Objectives: The current study aimed to evaluate the acute and chronic effects of smoking on the left and right ventricular (RV) diastolic function.

Patients and Methods: One hundred healthy male, 50 smokers and 50 non-smokers, underwent echocardiography, before smoking and 5 and 30 minutes after it to compare diastolic function of left ventricular (LV) and RV and examine the chronic and acute effects of smoking.

Results: Atrial late diastolic mitral inflow velocity (A_m) Atrial and late diastolic septal mitral annular velocity (a_{ms}) were high in smokers in comparison to those of the control group before smoking, but there was no difference in tricuspid diastolic parameters. Five minutes later, isovolumetric relaxation time (IVRT) was prolonged and a_{ms} further increased as a sign of LV diastolic dysfunction. Similar changes occurred in RV, in favor of acute RV diastolic dysfunction. After 30 minutes, early diastolic tricuspid inflow (E') decreased and a_{ms} and late diastolic tricuspid inflow (A') remained high. After five minutes, diastolic blood pressure increased, but returned to normal state after 30 minutes. Pulmonary arterial pressure did not change before and after smoking.

Conclusions: Chronic smoking caused left ventricular diastolic dysfunction. Acute intake caused left and right ventricular diastolic dysfunction. Changes persisted up to 30 minutes after smoking, although diastolic blood pressure returned to normal state.

Keywords: Cigarettes; Left Ventricular Diastolic Function; Right Ventricular Diastolic Function; Echocardiography

1. Background

One billion people in the world are addicted to cigarettes (1). Over five million people in the world die due to smoking and related illnesses yearly (2). In America, 20.5% of adults are smokers, and smoking annually causes one of five deaths (3). Epidemiological studies show that more than one out of 10 cases of cardiovascular deaths, (which include 54% of all deaths), is due to cigarettes worldwide (4).

Despite the identification of smoking as a major risk factor of atherosclerosis, its effect on the initiation and progression of cardiac systolic and diastolic dysfunction remains unknown (5). In young people, left ventricular (LV) diastolic dysfunction, observed in echo, is associated with increased morbidity and mortality rates, and it can be prevented by identifying the risk factors (6). On the other hand, diastolic dysfunction reduces the exercise capacity, neurohormonal activation and quality of life (7).

To investigate the chronic effects of smoking, Eroglu et

al. evaluated 80 healthy people, 40 smokers and 40 non-smokers, with a mean age of 26 years, by Doppler myocardial imaging and concluded that systolic and diastolic functions of the left and right ventricle change by smoking (8).

Alam et al. studied the acute effects of smoking on LV function in 36 healthy people (13 smokers and 23 non-smokers with a mean age of 38 years). Before, immediately and 30 minutes after smoking a cigarette containing 1.1 mg of nicotine, patients underwent an echo test. Transmitral flow velocity and left ventricular wall function were measured using the tissue Doppler imaging (TDI) method, and a mean of the four walls was measured to assess the left ventricular function. Immediately after smoking, the heart rate (HR) increased. After cigarette smoking LV diastolic function declined. Changes of velocity stayed even for 30 minutes later. The results were similar in smokers and non-smokers (9).

In a study by Kasikcioglu et al. after smoking two cigarettes, 10 male smokers aged 30 - 48 years underwent the TDI echocardiography: Daily smoking was more than 10 threads and all of them had a smoking history of at least five years. They had not smoked for eight hours before the study, in order to avoid possible residual effects. People with a history of hypertension, obesity, diabetes and hyperlipidemia, were excluded. In these cases coronary flow velocity reserve (CFVR) in the left anterior descending coronary artery was measured transthoracically by echo. After consumption of cigarettes, the blood pressure and HR increased. After smoking, the CFVR and right ventricular diastolic function declined. This study concluded that changes in right ventricular function are possibly due to the change in the CFVR (10).

Ilgenli et al. studied 20 healthy young men, who had an average smoking history of eight years. In a closed room, the subjects consumed cigarette content in a sitting position for five minutes. Before and after smoking, blood pressure, HR and trans-mitral and tricuspid flow parameters were measured by Echo. Basic results obtained 5, 15, 30, and 60 minutes after smoking were compared. Significant changes in left ventricular diastolic function, and mitral regurgitation were not observed by Transmitral Doppler (TMD) echocardiography, but the diastolic function of the RV was clearly impaired. Pulmonary artery pressure (PAP) obviously increased. After 30 minutes all changes returned to the base line (11).

Lichodziejewska et al. examined 66 patients under 40 years (33 smokers and 33 non-smokers) with a body mass index (BMI) < 25 by echocardiography. Smokers underwent echo again after smoking a single cigarette and their RV and LV diastolic functions were studied. HR increased immediately after smoking. There was LV diastolic dysfunction in smokers before and after smoking. In the smokers, early diastolic tricuspid inflow velocity/late diastolic tricuspid inflow velocity ratio (E_t/A_t) decreased, which indicated the right ventricular diastolic dysfunction in acute form (12).

Ali Dogan et al. investigated the LV diastolic function in 61 non-smokers, passively exposed to smoke. Two-dimensional echo, simple Doppler, and TDI were performed. Carboxyhemoglobin levels were measured before and after contact with cigarette smoke in a closed room echocardiography variables, HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and carboxyhemoglobin level were compared. Carboxyhemoglobin level increased, and LV diastolic function declined (13).

In previous studies mostly LV diastolic function was evaluated, but diastolic function of the RV was less considered. Some studies examined only chronic effects of cigarette, and if the acute diastolic function was considered, they used only mitral flow velocity and simple Doppler study, which is not enough to evaluate the diastolic function.

Some other studies measured the echo variables only once after smoking and persistence of changes was ignored. Some studies did not consider a certain age and

gender, but age and gender have known effects on diastolic function; some studies were performed in a closed space that may change nicotine level in blood.

2. Objectives

The current study aimed to determine the chronic and acute effects of smoking on diastolic LV and especially RV function in healthy young males, in open space by TDI and simple Doppler study.

3. Patients and Methods

3.1. Study Population

Inclusion criteria were: age less than 40 years old; BMI < 25; healthy men with normal clinical examination; normal heart Electrocardiography (ECG) and normal echocardiography; smokers had a smoking history of more than five years and consumed at least five cigarettes per day.

Exclusion criteria were: a history of hypertension; diabetes; hyperlipidemia; hypothyroidism; and hyperthyroidism; chronic use of alcohol and drugs; a history of valvular and coronary disease. The case and control groups were matched in terms of age and BMI and risk factors.

3.2. Equipment

Echocardiography was taken by the GE-Vingmed Ultrasound, Horten, Norway; model: VIVID 3n, class I, Type BF using probe transducer 3 Hz device.

3.3. Measurements

Echocardiography was done in a left lateral decubitus position. In the apical four chamber view, the pulse Doppler markers were placed respectively in the mitral and tricuspid tip, and velocity of blood flow in the beginning of diastole (E wave) and end of the diastole (A wave), deceleration time of early diastolic mitral inflow (DT), the early and late diastolic velocity ratio (E/A) were recorded. Also, PAP was measured by Doppler study of tricuspid valve.

In apical five chambers view, the isovolumic relaxation time (IVRT) was measured by pulse wave Doppler. All the volunteers were examined with online TDI mode as well so that a^{ml} (late diastolic lateral mitral annular velocity), e^{mL} (early diastolic lateral mitral annular velocity), a^{ms} (late diastolic septal mitral annular velocity), e^{ms} (early diastolic septal mitral annular velocity), a_t and e_t were calculated by placing the Doppler cursor on lateral and septal walls of the left ventricle and free wall of right ventricle.

3.4. Design

The simple random sampling method was used to select the sample. To prevent the Potential residual effects, smokers had not smoked for two hours before echocardiography. After a 10-minute rest, SBP and DBP and HR were recorded. Echocardiography was done for all sub-

jects by the same cardiologist (to avoid interpersonal error). Parameters were measured and recorded. Smokers consumed a cigarette (containing 0.45 mg of nicotine) in an open space. Five and 30 minutes later they underwent echo again and in every step their blood pressure and HR and echo parameters were recorded but nonsmokers were evaluated just once.

3.5. Data Analysis

The collected data were analyzed using SPSS software. Descriptive data were expressed in tables and charts and the quantitative indicators as mean $\pm$ SD. variables of the control group were compared with those of the smokers group using independent sample T-test. Univariate analysis of variance was used to remove the effect of the confounding factors, including heart rate and systolic and diastolic blood pressure. The effect of the number and duration of smoking on echocardiography variables and vital signs in smokers were checked by the Pearson correlation coefficient test.

To compare the variables in the smokers group the paired T-test was used five minutes before smoking and 30 minutes after smoking. When the paired T-test default was not established, their comparable non-parametric test i.e., Wilcoxon test was used, which was true about the variables of diastolic blood pressure. Level of significance was considered as $P < 0.05$.

3.6. Consideration of Ethical Issues

The current study was approved by ethical committee of Ahvaz Jundishapur university of medical sciences (Ref. No. ETH-706). All subjects voluntarily enrolled. The process explained and written consent was obtained from all participants. Echocardiography was performed free of charge.

4. Results

Table 1 shows demographic data. There is no significant difference between averages of the age, height, weight, BMI and HR in the control and smokers groups ($P = 0.49$, $P = 0.07$, $P = 0.90$, $P = 0.90$ and $P = 0.12$, respectively) but the average of systolic and DBP in smoker group was significantly more than that of the control group ($P = 0.01$ and $P = 0.02$, respectively) (Table 1).

The smokers consumed an average of 13.36 cigarettes per day and the average smoking duration was 9.58 years. In the comparison of diastolic function between the smoker group before smoking and control group, there was significant increase in variables of LV diastolic function of left ventricle containing late diastolic mitral inflow velocity (A_m) and late diastolic septal mitral annular velocity (a_{ms}) ($P = 0.04$ and $P = 0.05$, respectively) in the smoker group, but there was no significant difference regarding the diastolic function of right ventricle. To remove the effect of confounding factors, including heart rate and systolic and diastolic blood pressure, data were

analyzed one more time with a univariate analysis of variance and differences of parameters were still significant (Tables 2 and 3).

The effects of the number and duration of smoking on vital signs and variables of left and right ventricular diastolic function in smokers were assessed using a Pearson correlation coefficient test. Increasing the number of smoking increased the HR and end diastolic mitral flow velocity (A_m) ($P = 0.03$ and $P = 0.02$, respectively).

To study the acute effects of smoking, the vital signs before smoking and five minutes after it were compared using paired T-test. The HR and DBP increased significantly ($P = 0.02$) five minutes after smoking, but it had no confounding effect on echocardiographic variables ($P = 0.50$) after checking with the single-variable ANOVA test.

Five minutes after smoking a cigarette, IVRT and a_{ms} increased in the smoker group ($P = 0.05$ and $P = 0.007$, respectively), which were the symptom of LV diastolic dysfunction. Also, E_t decreased ($P = 0.02$) and A_t increased ($P = 0.04$) that indicates RV diastolic dysfunction (Table 3).

There was no significant difference between vital signs before and 30 minutes after smoking. The a_{sm} remained high ($P = 0.007$) that was a sign of stability of LV diastolic dysfunction after 30 minutes. The E_t remained still low ($P = 0.25$) and A_t remained high ($P = 0.046$) that were the signs of RV diastolic dysfunction stability after half an hour (Tables 3 and 4).

To verify the significance of the changes during 30 minutes the data were analyzed before smoking and five and 30 minutes after it using repeated measurement test. It was demonstrated that changes of HR, DBP, IVRT, a_{ms} , E_t , A_t were significant in half an hour ($P = 0.03$, $P = 0.02$, $P = 0.01$, $P = 0.02$, $P = 0.02$ and $P = 0.006$, respectively). The values of the PAP in the participants and their changes during the study were not significant.

Table 1. A Comparison Between Baseline Characteristics of the Subjects ^{a,b}

Variable, Unit	Control	Smokers	P Value
Age, y	30.84 $\pm$ 5.86	30.1 $\pm$ 4.77	0.49
Height, cm	176.42 $\pm$ 6.05	177 $\pm$ 1.35	0.07
Weight, kg	73.06 $\pm$ 6.83	72.90 $\pm$ 6.35	0.9
BMI, kg/m ²	23.43 $\pm$ 1.37	23.26 $\pm$ 1.46	0.09
HR, BPM	73.32 $\pm$ 5.58	75.1 $\pm$ 5.86	0.123
SBP, mmHg	111 $\pm$ 7.49	114.1 $\pm$ 5.86	0.02 ^c
DBP, mmHg	68.3 $\pm$ 6.82	71.5 $\pm$ 6.48	0.01 ^c

^a Values are presented as mean $\pm$ SD.

^b Abbreviations: BMI, body mass index; BPM, beat per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure; SD, standard deviation.

^c Shown in the text

Table 2. A Comparison Between Echocardiography Variables in the Study Groups ^{a,b}

Variable ,Unit	Control	Smokers Before Taking a Cigarette	P Value	Variance
E _m , cm/s	77.48 ± 16.74	79.24 ± 20.55	0.64	0.61
A _m , cm/s	51.86 ± 13.45	56.12 ± 13.87	0.12	0.050 ^c
E _m /A _m	1.51 ± 0.38	1.50 ± 0.34	0.90	0.55
IVRT, Msec	78.94 ± 12.58	77.88 ± 9.08	0.63	0.64
DT, Msec	199.60 ± 52.35	185.64 ± 42.14	0.14	0.081
E _{ml} , cm/s	14.1 ± 3.68	14.2 ± 3.48	0.88	0.80
A _{ml} , cm/s	8.26 ± 7.73	7.48 ± 2.1	0.49	0.70
E _{ms} , cm/s	10.82 ± 2.59	10.48 ± 2.02	0.46	0.37
A _{ms} , cm/s	7.66 ± 1.54	8.5 ± 2.44	0.043	0.027 ^c
E _t , cm/s	58.78 ± 11.12	59.26 ± 10.37	0.82	0.64
A _t , cm/s	40.46 ± 9.3	40.06 ± 10.38	0.84	0.96
E _t /A _t	1.52 ± 0.28	1.54 ± 0.24	0.60	0.61
E _t , cm/s	12.62 ± 3.23	12.1 ± 3.5	0.44	0.48
a _t , cm/s	12.06 ± 4.04	10.66 ± 3	0.052	0.11

^a Values are presented as mean ± SD.^b Abbreviations: A_m, late diastolic mitral inflow velocity; a_{ml}, late diastolic lateral mitral annular velocity; a_{ms}, late diastolic septal mitral annular velocity; a_t, late diastolic free wall tricuspid annular velocity; A_t, late diastolic tricuspid inflow velocity; DT, deceleration time of early diastolic mitral inflow; E_m, early diastolic mitral inflow velocity; e_{ml}, early diastolic lateral mitral annular velocity; e_{ms}, early diastolic septal mitral annular velocity; E_t, early diastolic tricuspid inflow velocity; e_t, early diastolic free wall tricuspid annular velocity; IVRT, Isovolumetric relaxation time.^c Shown in the text.**Table 3.** A Comparison Between echo Parameters Before and Five Minutes After Smoking a Cigarette ^{a,b}

Variable, Unit	Before Smoking	Five Minutes After Smoking	P Value
E _m , cm/s	79.24 ± 20.55	76.4 ± 16.25	0.29
A _m , cm/s	56.12 ± 13.87	55.34 ± 12.67	0.68
E _m /A _m	1.5 ± 0.34	1.42 ± 0.32	0.17
IVRT, Msec	77.88 ± 9.08	81.02 ± 10.79	0.05 ^c
DT, Msec	185.64 ± 42.14	192.44 ± 55.32	0.45
E _{ml} , cm/s	14.2 ± 3.48	13.92 ± 3.42	0.53
A _{ml} , cm/s	7.48 ± 2.1	7.32 ± 2.34	0.66
E _{ms} , cm/s	10.48 ± 2.02	10.38 ± 2.14	0.68
A _{ms} , cm/s	8.5 ± 2.44	8.96 ± 2.05	0.007 ^c
E _t , cm/s	59.26 ± 10.37	50.92 ± 9.74	0.02
A _t , cm/s	40.06 ± 10.38	41.06 ± 8.98	0.04 ^c
E _t /A _t	1.54 ± 0.24	1.49 ± 0.21	0.21
E _t , cm/s	12.1 ± 3.5	11.94 ± 3.55	0.72
a _t , cm/s	10.66 ± 3	10.94 ± 3.94	0.60

^a Values are presented as mean ± SD.^b Abbreviations: A_m, late diastolic mitral inflow velocity; a_{ml}, late diastolic lateral mitral annular velocity; a_{ms}, late diastolic septal mitral annular velocity; a_t, late diastolic free wall tricuspid annular velocity; A_t, late diastolic tricuspid inflow velocity; DT, deceleration time of early diastolic mitral inflow; E_m, early diastolic mitral inflow velocity; e_{ml}, early diastolic lateral mitral annular velocity; e_{ms}, early diastolic septal mitral annular velocity; E_t, early diastolic tricuspid inflow velocity; e_t, early diastolic free wall tricuspid annular velocity; IVRT, Isovolumetric relaxation time.^c Shown in the text.

Table 4. A Comparison Between Echo Parameters Before and 30 Minutes After Smoking a Cigarette ^{a,b}

Variable, Unit	Before Smoking	Thirty Minutes After Smoking	P Value
E _m , cm/s	79.24 ± 20.55	76.76 ± 18.57	0.38
A _m , cm/s	56.12 ± 13.87	56.38 ± 12.45	0.88
E _m /A _m	1.50 ± 0.34	1.39 ± 0.34	0.09
IVRT, Msec	77.88 ± 9.08	79.72 ± 11.20	0.34
DT, Msec	185.64 ± 42.14	194.28 ± 57.85	0.42
E _{ml} , cm/s	14.2 ± 3.48	14.58 ± 3.36	0.36
A _{ml} , cm/s	7.48 ± 2.1	7.64 ± 2.21	0.68
E _{ms} , cm/s	10.48 ± 2.14	10.04 ± 2.08	0.16
A _{ms} , cm/s	8.5 ± 2.44	8.7 ± 1.75	0.007 ^c
E _t , cm/s	59.26 ± 10.37	58.01 ± 10.91	0.025 ^c
A _t , cm/s	40.06 ± 10.38	43.5 ± 9.93	0.046 ^c
E _t /A _t	1.54 ± 0.24	1.49 ± 0.27	0.27
E _f , cm/s	12.1 ± 3.5	11.5 ± 4.14	0.31
A _f , cm/s	10.66 ± 3	11.54 ± 3.42	0.06

^a Values are presented as mean ± SD.

^b Abbreviations: A_m, late diastolic mitral inflow velocity; a_{ml}, late diastolic lateral mitral annular velocity; a_{ms}, late diastolic septal mitral annular velocity; a_t, late diastolic free wall tricuspid annular velocity; A_t, late diastolic tricuspid inflow velocity; DT, deceleration time of early diastolic mitral inflow; E_m, early diastolic mitral inflow velocity; e_{ml}, early diastolic lateral mitral annular velocity; e_{ms}, early diastolic septal mitral annular velocity; E_t, early diastolic tricuspid inflow velocity; e_f, early diastolic free wall tricuspid annular velocity; IVRT, Isovolumetric relaxation time.

^c Shown in the text.

5. Discussion

The current study measured the acute and chronic effects of smoking on left and RV diastolic functions by evaluation of the velocity of the mitral blood flow as well as TDI ECG. Moreover, confounding effects of the HR and DBP and SBP were excluded.

Chronic consumption of cigarettes affects the lipid metabolism, serum levels of clotting factors, reduces the blood flow, impairs the flexibility of red blood cells and atrial fibrosis (14). It also causes aging of the myocyte due to oxidative stress (15). Nicotine is toxic to cardiac fibroblasts (16).

Acute effects of nicotine include increase in myocardial oxygen demand, coronary vascular tone mediators, increasing the heart rate, and systemic blood pressure but decreasing the coronary blood flow and coronary flow reserve (17). Acute cigarette consumption temporarily reduces nitrate, nitrite and concentrations of antioxidants in plasma that is associated with the high blood pressure and higher HR. Increased arterial stiffness has been also reported (14).

Diastolic dysfunction is an independent factor for heart failure (18) and is an important component in the pathophysiology of heart failure even with normal systolic function (19). It is also associated with reduced activity potential (20). The prevalence of diastolic dysfunction in different societies is from 11% to 35% based on methodological and cohort study (20-22).

Abnormalities in diastolic filling play an important

role in clinical signs and prognosis of patients with heart diseases (23, 24). It can be studied easily and precisely by echocardiography (25). Echocardiography diastolic parameters such as, early and late diastolic velocity ratio E/A ratio, and DT have prognostic values in different circumstances. Diastolic dysfunction has also been a sign of poor prognosis even in asymptomatic patients (26).

Relaxation speed in males and females, even in the absence of cardiovascular disease decreases with age increase (27, 28). Doppler echocardiography is used to assess relaxation. If LV relaxation is impaired but left atrial pressure is not elevated, slower reduction of LV pressure, leads to decrease in early diastolic filling velocity (E) and increase in the time of early diastolic filling DT.

If the left atrial pressure increases, profile of filling velocity is falsely normalized (29). The measurement of the mitral and tricuspid annulus velocity in diastole using TDI (30) indicates left and right ventricular diastolic relaxation independent of the pre-load (20, 31-33). This method is comparable to angiography (34) and radionuclide techniques (34-36).

In the comparison of echocardiography variables between smokers (before smoking) and the control group, a_{ms} and A_m were significantly high in smokers that indicated chronic LV diastolic dysfunction even after removing the SBP effect. Diastolic function of the right ventricle was no significantly difference between the smokers before smoking and the control group.

It was found that the left ventricular diastolic function in chronic consumption of cigarettes was depressed, which was similar to that of the study by Eroglu (8) and Lichodziejewska et al. studies (12); but unlike those studies there was no chronic RV diastolic dysfunction.

The increased number of cigarettes raises the basic HR after smoking and increases A_m before smoking. More nicotine intake has more harmful effects on vital signs and diastolic function.

To investigate the acute effects of smoking, echocardiography variables were compared before and five minutes after smoking a cigarette. Five minutes after smoking, IVRT and a_{ms} increased that showed the decrease of LV diastolic function by both TDI and Doppler echocardiogram. In the current study, changes were evident in valve Doppler and TDI similar to those of Alam et al. (9) and Dogan (13), although the studies by Lichodziejewska (12) showed changes only in valves Doppler. In the study by Ilgenli changes were evident by TDI (11).

Five minutes after taking a cigarette E_t reduced and A_t significantly rose that indicates the reduction of RV diastolic function, similar to those of Kasikcioglu (10) and Lichodziejewska (12) results. RV diastolic dysfunction was attributed to rise of PAP in the study by Ilgenli (11). In the current study PAP changes were negligible and diastolic dysfunction cannot be affected by it.

However, DBP significantly increased five minutes after smoking, but had no confounding effects on the echocardiography variables.

To investigate the duration of diastolic changes, echocardiography variables were compared before and 30 minutes after smoking. There was no difference in HR and systemic blood pressure.

Among the LV diastolic function parameters, increase of a_{ms} remained significant after 30 minutes similar to that of the studies by Alam (9) and this disorder was not justified by confounding factors.

Decrease of E_t and increase of A_t remained after 30 minutes, in favor of persistent RV diastolic dysfunction. This finding was different from those of the study by Ilgenli (11), in which all changes reversed to baseline after half an hour.

Among the LV diastolic function variables, the IVRT increased five minutes after smoking and returned to baseline after 30 minutes, but a_{ms} changes persisted after half an hour. It may be due to more sensitivity of TDI to exploring diastolic changes compared to the simple Doppler study. The PAP changes during the study were minimal.

The amount of nicotine per cigarette in the current study was less than that of the previous studies, which indicated that even low doses of nicotine can induce diastolic dysfunction. Using both simple Doppler and TDI echo for a more Precise study, evaluation of both LV and RV, reevaluation of findings 30 minutes later make the current study different from previous surveys. In addition limitation of samples to males and young adults in order to refuse gender and age impression on diastolic

function can make the obtained results more powerful than those of the others.

The findings suggest that chronic consumption of cigarettes causes LV diastolic dysfunction and the amount of smoking in a day has a direct relationship with intensity of disorder. Acute consumption of cigarette induces diastolic dysfunction in both ventricles which persists after 30 minutes in RV.

Acknowledgments

Authors acknowledge their gratitude to Ahvaz Jundishapur university of medical sciences for the financial support to conduct this research project. Authors' specially thank members of the atherosclerosis research center and the Golestan hospital clinical development research unit for their contributions.

Authors' Contributions

Study concept, design and Scientific Content: Seyed Masoud Seyedian and Farzaneh Ahmadi. Acquisition of relevant references: Seyed Masoud Seyedian and Shahla Majididi; data collection, data Analysis and manuscript preparation: Farzaneh Ahmadi, Lida Asgharinejad, Mehrnoush Esmaeili, and Molook Salehzadeh; critical revision of the manuscript for important intellectual content: Seyed Masoud Seyedian and Farzaneh Ahmadi; approval of the final version: Seyed Masoud Seyedian; interpretation of results: Seyed Masoud Seyedian, Shahla Majididi and Farzaneh Ahmadi; drafting the article: Lida Asgharinejad Mehrnoush Esmaeili and Molook Salehzadeh; Administrative, technical, and material support: Ahvaz Jundishapur University of Medical Sciences; revising the article: Seyed Masoud Seyedian; Study supervision and Corresponding Author: Farzaneh Ahmadi and submitting the paper: Molook Salehzadeh.

Funding/Support

Financial support of this study was provided by Ahvaz Jundishapur University of Medical Sciences.

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