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The effect of smoking on cardiac diastolic parameters including Vp, a more reliable and newer parameter

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Abstract

Background: *Previous studies have focused mainly on the acute effects of smoking on the diastolic function of the heart. The present study was conducted to demonstrate the chronic effects of smoking on the diastolic functional parameters of the heart, including transmitral M- mode coloured flow propagation velocity (Vp), among relatively younger asymptomatic adults.*

Method: *Hundred smokers with histories of incessant smoking for at least one year prior to the time of the investigation were included in the prospectively designed study as group I. Group II consisted of 35 non-smokers, matched for age and gender. Addiction to smoking was graded according to the modified Fagerström test for nicotine dependence (M-FNDT). Each smoker was designated by a nicotine dependence index (NDI) according to the M-FNDT. Groups I and II were compared with respect to major diastolic functional parameters on transthoracic echocardiography (TTE), including the E/A ratio, deceleration time (DT), isovolumic relaxation time (IVRT) and Vp, along with basic clinical and echocardiographic parameters.*

Results: *Thirty one smokers in group 1 and 5 non-smokers in group 2 were excluded from the study according to the pre-defined exclusion criteria. Therefore 69 smokers (mean age: 30 ± 4.9 years, M/F: 32/37) in group I were compared with 30 non-smokers (mean age: 31.4 ± 4.8 years, M/F: 15/15) in group II. In group I the mean values of E/A and Vp were significantly lower ($p < 0.001$), whereas the mean values of IVRT and DT were significantly higher ($p < 0.001$) than in group II. In group I the value of NDI was positively correlated with the values of DT and IVTR ($p < 0.001$) and negatively correlated with the value of Vp ($p < 0.001$).*

Conclusion: *Conventional and relatively new parameters of cardiac diastolic function, in particular Vp, were found to be impaired in smokers demonstrating the chronic adverse effects of smoking on the diastolic function of the heart. The severity of this impairment was closely correlated with the degree of addiction to smoking.* (Cardiol J 2007; 14: 281–286)

Key words: smoking, left ventricular diastolic dysfunction, nicotine dependence index

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Introduction

Diastolic dysfunction is characterised by impaired left ventricular (LV) filling and generally correlates well with ageing [1]. The relaxation process is closely associated with active relaxation and passive chamber stiffness, the latter, in particular, emerging as more important towards the end of diastole [2]. Factors interfering with diastolic function generally interact with one of these two indices or both. Diastolic dysfunction of the abnormal relaxation type is particularly due to impairment of active relaxation and, to a lesser extent, increased chamber stiffness. Echocardiographic features of abnormal relaxation are prolongation of isovolumic relaxation time (IVRT), prolongation of deceleration time (DT), reversal of the E/A ratio, in which the E wave is normally higher than the A wave, and reduction in the value of transmitral M-mode coloured flow propagation velocity (Vp). Vp is a relatively new parameter typically based on early diastolic intraventricular pressure gradients (IVPG) [3] between the mitral valve and the apex of the heart. Vp is therefore considered an efficiency index of early diastolic filling. In contrast to the conventional diastolic functional parameters, Vp is, to a large extent, regarded as a preload-independent index of diastolic performance [4] and is considered a more reliable parameter.

Smoking has numerous adverse effects on various organ systems. Previous studies have focused particularly on the acute effects of smoking on the diastolic function of the heart. In the present study we have tried to investigate the presence of diastolic dysfunction (of abnormal relaxation type) among relatively young and healthy chronic smokers.

Method

Hundred smokers with histories of incessant smoking for at least one year prior to the investigation were included in the prospectively designed study as group I. The degree of addiction to smoking was graded according to the modified Fagerström test for nicotine dependence (M-FNDT) (Table 1) [5]. Each smoker was allocated a nicotine dependence index (NDI) according to M-FNDT. Group I was compared with group II, consisting of 35 non-smokers, with respect to major diastolic functional parameters on transthoracic echocardiography (TTE), including ratio of E/A, DT, IVRT and Vp. The two groups were also compared with respect to other conventional echocardiographic parameters, including LV end-diastolic diameter (LVEDD), end-diastolic interventricular septum thickness (EDIVST), end-diastolic LV posterior wall thickness (EDPWT), left atrial diameter (LAD) and LV ejection fraction (LVEF), along with the basic clinical parameters of heart rate (HR), systolic and diastolic blood pressure (BP) and body mass index (BMI). Heart rate and blood pressure were measured 10 minutes prior to echocardiographic examination. Both smokers and non-smokers were selected from a group of healthy volunteers of the same ethnic background.

The presence of the following potential causes of diastolic dysfunction were accepted as exclusion criteria: age > 40, hypertension, infiltrative diseases, history or evidence of coronary artery disease and echocardiographic evidence of LV hypertrophy, systolic dysfunction, wall motion abnormalities or pericardial disease. In some instances an abnormal relaxation pattern may be

Table 1. Modified Fagerström test for nicotine dependence.

1. How soon after you wake up do you smoke your first cigarette?
   - ☐ Within 5 minutes (3 points)
   - ☐ 5 to 30 minutes (2 points)
   - ☐ 31 to 60 minutes (1 point)
   - ☐ After 60 minutes (0 points)
2. Do you find it difficult not to smoke in places where you shouldn't, such as in church or school, in a movie, at the library, on a bus, in court or in a hospital?
   - ☐ Yes (1 point)
   - ☐ No (0 points)
3. Which cigarette would you most hate to give up; which cigarette do you treasure the most?
   - ☐ The first one in the morning (1 point)
   - ☐ Any other one (0 points)
4. How many cigarettes do you smoke each day?
   - ☐ 10 or fewer (0 points)
   - ☐ 11 to 20 (1 point)
   - ☐ 21 to 30 (2 points)
   - ☐ 31 or more (3 points)
5. Do you smoke more during the first few hours after waking up than during the rest of the day?
   - ☐ Yes (1 point)
   - ☐ No (0 points)
6. Do you still smoke if you are so sick that you are in bed most of the day, or if you have a cold or the flu and have trouble breathing?
   - ☐ Yes (1 point)
   - ☐ No (0 points)

Scoring: 7 to 10 points — highly dependent; 4 to 6 points — moderately dependent; fewer than 4 points — minimally dependent.

complicated by conditions with considerably elevated LV filling pressures, such as mitral regurgitation or congestive heart failure causing a mitral flow pattern termed "pseudo normalisation" with a taller E wave and a shorter A wave [6]. Cases with potential causes of pseudo normalisation were therefore excluded from the study. Cases with restrictive patterns (a considerably taller E wave with a reduced A wave), with moderate-to-severe degrees of valvular regurgitation or stenosis on TTE, cases with chronic morbidities, including diabetes mellitus, bronchial asthma, chronic hepatitis or renal failure and cases on chronic medication or evidencing any form of dependence, for example on alcohol, cocaine or other drugs, were also excluded. Cases were referred to other departments for diagnosis where particular conditions were indicated. Smokers and non-smokers were subject to the same exclusion criteria. The exercise stress test was performed in all cases at least 12 hours prior to the TTE examination. Patients with abnormal initial ECG (indicating ischaemia or strain, for example), patients with positive maximal exercise stress tests (with probable coronary artery disease), and patients with submaximal tests (those that did not achieve the target heart rate) were also excluded from the study.

TTE examination in group I was performed after an abstinence from smoking ranging between 6 h and 48 h, depending on the compliance of the smokers, to obviate the acute effects of smoking on echocardiographic parameters. For the majority of smokers the abstinence period exceeded 24 h. Only 15 smokers abstained for less than 12 h, the minimum period being 6 h. Echocardiographic examination was performed by the same single observer, who was not informed of the study design or the smoking status of the patients.

GE Vingmed Vivid 4 with a 3 MHz transducer was used for echocardiographic evaluation. The measurements were performed according to the proposals of the American Association of Echocardiography [7]. In the apical four-chamber pulsed wave Doppler (PW) was situated at the tips of mitral valves [8] to obtain early (E) and late (A) diastolic waves for the calculation of the ratio of E/A and DT, the interval between the peak and the end of the E wave, normal value: 179 ± 20 ms (< 50 years). Sample volume was oriented to a position between the LV outflow tract and mitral valve, where LV inflow and outflow velocities might be recorded simultaneously to measure IVRT, the interval between the end of LV outflow wave and the beginning of early mitral diastolic wave, normal value: 76 ± 11 ms (< 50 years). The measurement of Vp is a relatively new method used in the evaluation of diastolic function [9]. A coloured M-mode cursor was situated between the LV inflow tract and apex to measure Vp in the apical four-chamber view. The slope of the first red to blue colour transition (the aliasing velocity) on a plane 4 cm distal in the LV from the mitral valve plane was accepted as Vp [4], with values of < 55 cm/s and < 45 cm/s in young and middle aged adults respectively defining impaired relaxation [10]. LVEDD and LAD values were measured by M-mode in the parasternal long axis view. The LVEF value was measured by the modified Simpson method. The mean of the three consecutively measured values of each parameter (clinical and echocardiographic) was accepted as the final value characterising the patient.

Parametric data were expressed as mean ± ± standard deviation, and categorical data as percentages. SPSS 10.0 was used to perform statistical procedures. Parametric data were compared by Student's t test and categorical data by the χ^2 test. Correlations were searched by Pearson's correlation. A p value ≤ 0.05 was accepted as significant.

Results

According to the pre-defined exclusion criteria, 31 smokers were excluded from Group I and 5 non-smokers from group II. Therefore 69 smokers (mean age: 30 ± 4.9 years, 32 men and 37 women) in group I were compared with 30 non-smokers (mean age: 31.4 ± 4.8 years, 15 men and 15 women) in group II. There was no statistically significant difference between the two groups with regard to gender or mean age ($p > 0.05$). The mean values of systolic and diastolic BP, HR, BMI, LVEDD, EDIVST, EDPWT, LAD and LVEF did not differ significantly between the two groups either ($p > 0.05$). In group I the mean values of Vp, DT and IVRT and the ratio of E/A were 50.9 ± 17 cm/s, 246.6 ± 38.4 ms, 140 ± 18 ms and 1.1 ± 0.12 respectively, while the same mean values in group II were 110.7 ± 38.9 cm/s, 181.1 ± 24.9 ms, 98 ± 10 ms and 1.37 ± 0.1 respectively. In group I the mean values of E/A and Vp were significantly lower ($p < 0.001$), whereas the mean values of IVRT and DT were significantly higher ($p < 0.001$) than those in group II. The mean value of NDI in group I was found to be 6.01 ± 2.44, while the mean value of smoking duration in group I was 6.65 ± 4.09 years. In group I there were only 9 smokers who had smoked for 1 year while there were 46 smokers who had smoked for 5 years or more prior to the investigation. The comparison of

Table 2. Comparison of general and echocardiographic features between smokers and non-smokers.

	Group I (smokers) (n = 69)	Group II (non-smokers) (n = 30)	p value
Mean age [years]	30 ± 4.9	31.4 ± 4.8	NS
Gender (M/F)	32/37	15/15	NS
Body mass index [kg/m^2]	22.5 ± 3.8	23.4 ± 4.8	NS
Systolic blood pressure [mm Hg]	122 ± 9	115 ± 11	NS
Diastolic blood pressure [mm Hg]	75 ± 9	73 ± 7	NS
Heart rate [beat/min]	72 ± 13	68 ± 17	NS
LVEDD [cm]	4.4 ± 0.5	4.6 ± 0.65	NS
EDIVST [mm]	8.10 ± 1.60	7.93 ± 1.30	NS
EDPWT [mm]	7.80 ± 1.95	7.92 ± 1.58	NS
Left atrial diameter [cm]	3.7 ± 0.6	3.6 ± 0.5	NS
Left ventricular ejection fraction [%]	64 ± 9	66 ± 12	NS
E/A	1.10 ± 0.12	1.37 ± 0.10	< 0.001
Deceleration time [ms]	246.61 ± 38.49	181.14 ± 24.9	< 0.001
Isovolumic relaxation time [ms]	140 ± 18	98 ± 10	< 0.001
Vp [cm/s]	50.90 ± 17.07	110.73 ± 38.93	< 0.001
Nicotine dependence index	6.01 ± 2.44	–	–
Duration of smoking [years]	6.65 ± 4.09	–	–

M — male; F — female; LVEDD — left ventricular end-diastolic diameter; EDIVST — end-diastolic interventricular septum thickness; EDPWT — end-diastolic left ventricular posterior wall thickness; left atrial; E — early diastolic mitral flow rate; A — late diastolic mitral flow rate; Vp — transmitral M-mode coloured flow propagation velocity; NS — not significant

Table 3. Comparison of the values of diastolic parameters, nicotine dependence index (NDI) and duration of smoking between subgroups of smokers (highly, moderately and minimally dependent subgroups classified according to NDI values).

	Group A (NDI = 7–10) Highly dependent (n = 35)	Group B (NDI = 4–6) Moderately dependent (n = 22)	Group C (NDI < 4) Minimally dependent (n = 12)
E/A	0.91 ± 0.13*	1.25 ± 0.7	1.22 ± 0.9
Deceleration time [ms]	262.5 ± 32.5$^{+,\S}$	238.6 ± 12.4**	193.2 ± 18.2
Isovolumic relaxation time [ms]	153.6 ± 14.5$^{+,\S}$	137.5 ± 12.5**	109.2 ± 21.5
Vp [cm/s]	39.5 ± 8.5$^{+,\S}$	54.4 ± 6.5**	84.5 ± 11.95
Nicotine dependence index	8.20 ± 1.10$^{\#}$	5.04 ± 0.65§	1.9 ± 0.79
Duration of smoking [years]	6.83 ± 4.95	6.68 ± 3.98	6.50 ± 3.94

E — early diastolic mitral flow rate; A — late diastolic mitral flow rate; Vp — transmitral M-mode coloured flow propagation velocity; $^{*}p < 0.05$ *vs*. group B and group C; $^{+}p < 0.05$ *vs*. group B; $^{\S}p < 0.001$ *vs*. group C; $^{\#}p < 0.001$ *vs*. group B and group C; $^{**}p < 0.05$ *vs.* group C

general features and echocardiographic parameters between the two groups is shown in Table 2. Table 3 demonstrates a comparison of subgroups in group I with different NDI values (highly, moderately and minimally dependent groups classified according to M-FNDT). Except for the mean value of E/A compared between the moderately and minimally dependent subgroups ($p > 0.05$), the mean values of diastolic parameters and NDI differed significantly between the subgroups, whereas the duration of smoking did not differ significantly between the subgroups ($p > 0.05$).

In group I the value of NDI was positively correlated with the values of DT and IVTR ($r = 0.73$, $r = 0.67$ respectively, $p<0.001$) and negatively correlated with the value of Vp ($r = –0.90$, $p < 0.001$) (Fig. 1). The values of NDI and E/A were uncorrelated ($p > 0.05$).

Discussion

Diastolic dysfunction of the heart is generally defined as increased resistance to diastolic filling of part or all of the heart. Factors which may impair the

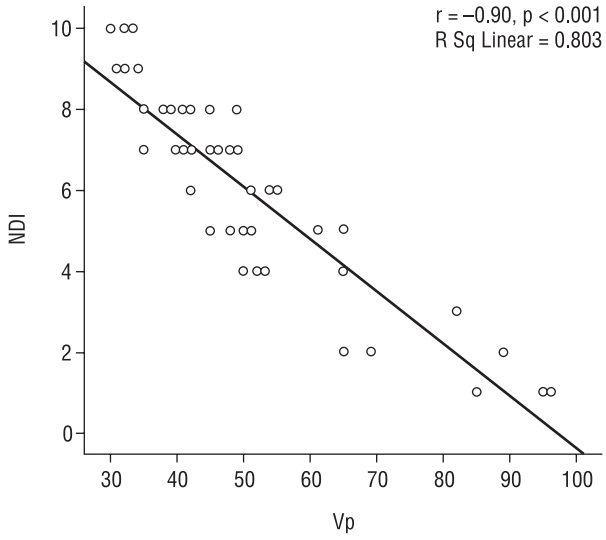

Figure 1. The negative correlation between the nicotine dependence index (NDI) and transmitral M-mode coloured flow propagation velocity (Vp).

diastolic function of the heart include coronary artery disease [11], infiltrative cardiac diseases such as amyloidosis, LV hypertrophy and pericardial diseases [12].

Smoking has numerous adverse effects on various organ systems, but the most adversely affected ones are the respiratory and circulatory systems. In addition to other well-documented harmful effects, smoking has been reported to have adverse effects on the diastolic function of the heart. Previous studies have mainly focused on the acute effects of smoking on diastolic function in different groups. Alam et al. [13] reported acute adverse effects of smoking on diastolic function by using conventional and mitral annular Doppler parameters in a group of 36 healthy participants. Kyriakides et al. [14] investigated the acute effects of smoking a single cigarette on diastolic function in a group of 20 patients with angiographically documented coronary artery disease by using conventional parameters and reported no prolongation of IVRT and DT values but a decrease in the ratio of E/A compared with the control group. Similarly, Stork et al. [15] reported acute adverse effects of smoking a single cigarette on diastolic function by using conventional parameters in a group of 28 smokers with documented coronary artery disease.

The present study also demonstrated the adverse effects of smoking on diastolic function of the heart, but the major difference from the abovementioned studies was the demonstration of the chronic adverse effects of smoking on diastolic function by using both conventional parameters and Vp in a larger population of relatively younger healthy smokers. Both conventional parameters and Vp, which is more reliable and preload-independent, worked well in demonstrating the chronic adverse effects of smoking on diastolic function.

There are possible explanations for the chronic adverse effects of smoking on the diastolic function of the heart, as demonstrated in the present study. Smoking has long been known to impair the structure of connective tissue in various organ systems. Increased arterial stiffness in smokers has been linked to structural alterations in the vascular media, including calcification [16], increased collagen and reduced elastin content [17]. Regardless of the presence of atherosclerosis, arterial and myocardial stiffness have been clinically important in smokers. In canine models exposed to nicotine, increased LV chamber stiffness was reported to be due to increased collagen deposition and collagen cross-links in the myocardium [18]. Fibrotic changes throughout the myocardium due to collagen deposition may impair diastolic function in smokers.

Impaired regulation of nitric oxide (NO) synthesis in the myocardium may be another possible mechanism explaining the impairment of relaxation in smokers. NO is synthesised via nitric oxide synthase (NOS). There are three known isoforms of NOS (NOS1, NOS2 and NOS3). Of these, NOS2 and NOS3 are known to be expressed in the human myocardium. NOS2 is an inducible isoform and is not normally expressed, whereas NOS3 is endothelial and is physiologically expressed in the normal myocardium. The amount of NO synthesised via NO3 is generally much lower. The lower physiological amount of NO has some beneficial effects, including an improvement in remodelling after myocardial infarction [19] and amelioration of ventricular relaxation (lusiotrophy). Smoking is a well-known factor that induces endothelial dysfunction through impairment of NO production [20, 21]. Smoking may also impair ventricular relaxation by inhibiting physiological expression of NO3 in the myocardium.

There may be clinical outcomes of asymptomatic diastolic dysfunction. The presence of diastolic dysfunction in an asymptomatic patient has been reported as a risk factor for the future development of heart failure [22]. In other terms, asymptomatic diastolic dysfunction may be an early marker of an increased risk of symptomatic heart failure and subsequent mortality. Patients with diastolic dysfunction are also considered to be susceptible to ventricular arrhythmias [23] and sudden cardiac death. An increased risk of arrhythmogenesis in

diastolic dysfunction may be due to myocardial fibrosis, increased sympathetic tone, changes in excitation-contraction coupling [23] and also to the minimal pathological changes in coronary microcirculation that do not induce documentable ischaemic changes [24]. In the present study these outcomes were not documented owing to the study design, but in long-term clinical follow-up smokers with asymptomatic diastolic dysfunction may be at increased risk for these outcomes.

In conclusion, the diastolic function of the heart was found to be impaired among relatively younger healthy smokers. The severity of this impairment was closely correlated with the degree of addiction to smoking. Further large-scale studies are required to confirm the present study. Healthy smokers with asymptomatic diastolic dysfunction may be at increased risk for future morbidities in long-term clinical follow-up. Long-term prospective studies based on follow-up of these patients are also warranted in order to clarify this issue.

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