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Acute effects on the ventricular function in Swedish snuffers: an echocardiographic study

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Summary

Aims: Cigarettes and Swedish snuff contain nicotine, which influence the cardiovascular system. Cigarette smoke has been shown to give an acute impairment in diastolic heart parameters. The systolic and diastolic heart function in snuff users is not thoroughly enough investigated. The aim of this study was to investigate if Swedish snuff will give an acute decrease in systolic and diastolic heart parameters in the left and right ventricles in healthy Swedish snuffers.

Methods and results: Thirty healthy volunteers were examined with echocardiography. The study involved recordings from four different times: before snuff intake, 5 and 30 min after intake and finally 30 min after snuff withdrawal. The systolic and diastolic heart parameters were collected with conventional echocardiographic methods. In addition, the heart frequency and blood pressure response were measured. The pulse and blood pressure response were significantly altered ($P<0{\cdot}01$) during the test. Left ventricular ejection fraction and the amplitudes of mitral and tricuspid annulus motion did not alter significantly. The main finding in the study was the significant decrease ($P<0{\cdot}05$) in several diastolic heart parameters for both the left and right ventricles.

Conclusions: This study shows that snuff intake causes a significant decrease in E/A ratio and a delay in ventricular relaxation and therefore a decrease in diastolic heart function in the left and right ventricles. The mechanism behind these alterations is probably very complex, but a combination of nicotine effects and loading conditions is probably the main factor.

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Introduction

It is generally accepted that smoking is a major risk factor for cardiovascular disease as it affects both the coronary arteries and peripheral vessels in the body (Prasad *et al.*, 2009). Cigarettes, which contain nicotine amongst many other components, affect the cardiovascular system in terms of morphological and biochemical disturbances in the endothelium (Hanna, 2006).

Smoking also gives an immediate rise in heart rate and blood pressure (Minami *et al.*, 1999). There are a number of studies showing that smoking also gives acute negative effects in diastolic heart function in both chronic smokers and in non-smokers (Alam *et al.*, 2002; Karakaya *et al.*, 2006; Gulel *et al.*, 2007; Ilgenli & Akpinar, 2007; Barutcu *et al.*, 2008; Ciftci *et al.*, 2008; Giacomin *et al.*, 2008). These studies show an acute significantly reduction of several diastolic parameters of both the left and right ventricles associated with smoking. Why and how the cardiac function is affected when smoking is not fully mapped and the mechanism is probably very complex.

In Sweden, snuff is an alternative to cigarettes for many people. Water is the main ingredient in snuff but it also contains tobacco (nicotine) and some other substances. Fant *et al.* (1999) show that snuff is capable of delivering large amounts of nicotine to the blood stream, even higher concentrations than cigarettes in some brands. They suggest that the cardiovascular hazards of smoking that may be related to nicotine also should be expected in snuff users (Fant *et al.*, 1999). There are a number of studies conducted to determine whether snuff really increases the risk of developing cardiovascular disorders in the same way that cigarette smoke does (Huhtasaari *et al.*, 1992; Bolinder *et al.*, 1994; Asplund *et al.*, 2003; Hergens *et al.*, 2007; Wennberg *et al.*, 2007; Janzon & Hedblad, 2009). These studies show broadly similar results, as they believe that snuff is not as dangerous as smoking in terms of cardiovascular disorders. They argue, however, that snuff users still have an increased risk to suffer from cardiovascular diseases compared to non-snuff users and non-smokers. Other studies have shown that snuff users also are at increased risk of developing hypertension (Hergens *et al.*, 2008).

However, what is still not investigated thoroughly enough is if snuff provides an acute impairment of cardiac diastolic parameters in the same way that cigarette smoke does. The purpose of this study is therefore to investigate if Swedish snuff will give an acute decrease in systolic and diastolic heart parameters in the left and right ventricles in healthy Swedish snuffers and if so, to examine how long this acute effect will last. The pulse and the blood pressure reaction in the subjects will also be examined.

Methods

Subjects

Thirty-one volunteers (27 men, four women) were examined with ultrasound of the heart at the Department of Clinical Physiology at the University Hospital in Örebro. Subjects were recruited amongst employees, friends and students. All the participants were consumers of snuff but to varying degrees. Only healthy persons with no history of cardiovascular disease and with a normal ultrasound of the heart with left ventricular ejection fraction (LVEF) > 50% were included in the study. One participant was excluded from the study because of a history of elevated blood pressure.

The participation in this study was voluntary. No non-snuffing persons were asked to participate in the study owing to the actual health hazards, which may be caused from snuff usage. Some basic characteristics and measured values are show in Table 1.

All of the volunteers had to read the information blanket posted to them in advance and also give us their approval before including them in our study. The study was approved by the regional ethical committee.

Study protocol

All volunteers had been instructed not to smoke or use snuff for at least 5 h before the examination. When the volunteers first came to the department, their weight and height were measured. Then the volunteers were told to lie down on the bed to rest for 10 min. After 10 min, the heart rate and blood pressure were measured. The subjects were examined with an echocardiograph (GE Vingmed Ultrasound A/S, Horten, Norway). The subjects were scanned before the study began to rule out any abnormalities. Normal LVEF was considered >50%. After the scan, all of the systolic and diastolic measurements from both the left and right ventricles were collected before the subjects put the snuff into their mouth. Heart rate was measured continuously during the examination with a handheld pulseoximeter (GE Datex Ohmeda Tuffsat, Louisville, KY, USA) and the blood pressure (in the right arm) was collected with an automatic sphygmomanometer (Omron Digital Blood Pressure Monitor HEM-907; Omron Healthcare, Kyoto, Japan). After the first examination of the systolic and diastolic measurements, the subjects were told to put a bag of snuff ('Ettan Original Portion', 8 mg g^{-1} nicotine) under their upper lip ('Ettan' is one of the leading brands of snuff in Sweden. We were not sponsored to use this brand). After 5 min, the same measurements of systolic and diastolic parameters were recorded and the heart rate and blood pressure response was noted. The next measurement was carried out 30 min after the volunteers put the snuff under their upper lip. After the third measurement, the subjects were told to take the bag of snuff out. Thirty minutes after the withdrawal of the snuff, one last measurement of the parameters were recorded as well as the heart rate and blood pressure response.

Table 1 Basic characteristics and echocardiographic data of the volunteers (n = 30).

	Mean ± SD
Age (years)	35 ± 11 (21–63)
Height (cm)	178 ± 8 (163–193)
Weight (kg)	79 ± 15 (57–123)
Left ventricular end diastolic diameter (mm)	51 ± 4 (44–59)
Left ventricular end systolic diameter (mm)	33 ± 4 (24–43)
Thickness septum end diastole (mm)	9 ± 1 (7–12)
Thickness posterior wall end diastole (mm)	8 ± 1 (6–10)
Left atrial area 4-chamber view systole (cm^2)	17 ± 3 (12–24)
Right atrial area 4-chamber view systole (cm^2)	16 ± 3 (12–24)
RVOT1 (mm)	30 ± 3 (23–35)
RVIT3 (mm)	34 ± 3 (25–37)
LVEF Simpson (%)	63 ± 5 (54–73)
TAM (mm)	24 ± 3 (19–31)

RVOT, right ventricular outflow tract; RVIT, right ventricular inflow tract; LVEF, left ventricular ejection fraction; TAM, tricuspid annulus motion.

Echocardiographic examination

The subjects were examined with an echocardiograph (GE Vingmed Ultrasound A/S) in the left lateral recumbent position using a phased array ultrasonic probe with Doppler tissue imaging (DTI) technology (M4S; GE Ultrasound, Phoenix, AZ, USA). Moving images were stored in sequences of three cardiac cycles each with optimization of frequency and gain. The Doppler measurements were stored within three RR intervals each with sample volume adjusted to 5·1 mm (default settings). In the DTI recordings, the filter settings were adjusted to at least 150 frame per seconds and gain was adjusted to the minimal optimal level. All measurements were performed during end-expiration for every subject to rule out any respiratory changes. All data were analysed using an Echopac (GE Vingmed Ultrasound A/S) Compaq DeskPro Workstation 300 (Compaq Computer Corporation, Houston, TX, USA). Data were stored as mean values of three measurements.

Measurements

Left ventricle

In the four-chamber view, the peak rapid filling velocity (E), peak atrial filling velocity (A), E-wave deceleration time (DT) and the E/A ratio were recorded through the mitral valve using

pulsed wave Doppler. Left ventricular isovolumetric relaxation time (IVRT) was recorded using pulsed wave Doppler in the five-chamber view. The 'sample volume' was placed between the aortic and the mitral valves. The longitudinal systolic motion of the septal, lateral, inferior and anterior walls was recorded in the four-chamber and two-chamber views, respectively using M-mode in the basal segments of the left ventricle. Also, the peak systolic (S) and peak early (é) and late (á) diastolic velocities in the myocardial walls were recorded in the four- and two-chamber views, respectively using pulsed wave DTI in the basal segments of the ventricle. The same registrations were also performed using color-coded DTI (CC-DTI). The Q-analysis (offline analysis of the CC-DTI recordings) was performed in the basal segments. LVEF was calculated using the modified biplane Simpson's rule, registered in the four- and two-chamber views, respectively.

Right ventricle

In parasternal short-axis view, a pulsed wave Doppler through the tricuspid valve recorded the peak rapid filling velocity (E), peak atrial filling velocity (A), E-wave DT and the E/A ratio. In the four-chamber view, the systolic longitudinal motion of the free lateral wall was recorded using M-mode. Pulsed wave DTI recorded the peak systolic (S) and the peak diastolic early (é) and late (á) myocardial velocities in the basal segment of the free lateral wall. The CC-DTI application was also recorded to measure the peak systolic and peak diastolic early and late myocardial velocities. The Q-analysis was performed in the basal segment of the free lateral wall.

Statistical analysis

Analysis of variance (ANOVA) for repeated measurements was used. Time was used as within factor at four levels. Bonferroni correction was done.

The statistical significance level was set to 5%. All data are presented as mean ± SD.

Shapiro–Wilks test for normal distribution for each cardiac parameter was performed. If the Shapiro–Wilks test was significant indicating non-normal distribution, a sensitivity test was done. The same ANOVA was then repeated without the outliers. In the tables, the ANOVA from the first analyses are presented and as footnotes the results from the Shapiro–Wilks and sensitivity analyses.

Data were analysed using the SPSS 17.0.2 statistical software (SPSS, Chicago, IL, USA).

Results

Time I is before snuff intake, time II is 5 min after snuff intake, time III is 30 min after snuff intake and time IV is 30 min after snuff withdrawal.

Heart rate and blood pressure response

The heart rate in the subjects did not alter significantly when snuff was put into the mouth, that is, from time I to time II. The heart rate did not either change significantly between time I and time III and between II and time III. What did occur was that the heart rate decreased significantly 30 min after snuff withdrawal comparing to the earlier three measurements (Table 2). The systolic blood pressure first decreased significantly immediately after snuff intake (time I versus time II). Thirty minutes after snuff intake there was a normalization of both the systolic and diastolic blood pressure, which were constant 30 min after snuff withdrawal (Table 2).

Left ventricular systolic function

As shown in Table 3, the global left ventricular systolic function did not alter significantly using moist snuff. Mitral annular motion (MAM) and LVEF remained unaltered during the test. Nevertheless, one regional significant decrease ($P = 0{\cdot}02$) in peak systolic longitudinal velocity in the myocardium recorded with pulsed wave DTI did occur in the septal wall (septal S).

Left ventricular diastolic function

Many measurements of the left ventricular diastolic function were performed. As shown in Table 4, significant alterations occurred in several measurements such as the mitral E/A ratio (E/A), the A-wave velocity (A) and the DT of the mitral valve, IVRT and the peak myocardial late diastolic velocity (mean four sites) measured with both pulsed wave DTI (á) and color-coded DTI (CC-DTI a).

Table 2 Heart rate and systolic and diastolic blood pressure response in 30 volunteers. Time I is before snuff intake, time II is 5 min after snuff intake, time III is 30 min after snuff intake and time IV is 30 min after snuff withdrawal.

Measurement $n = 30$	Time I	Time II	Time III	Time IV	I versus II	I versus III	I versus IV	II versus III	II versus IV	III versus IV
Heart rate (beats min^{-1})	63 ± 12	61 ± 11	63 ± 11	56 ± 9	ns	ns	P = 0·001	ns	P = 0·004	P<0·001
Blood pressure systolic (mmHg)	129 ± 16	121 ± 13	127 ± 12	126 ± 14	P<0·001	ns	ns	P = 0·004	P = 0·002	ns
Blood pressure diastolic (mmHg)	73 ± 12	71 ± 11	75 ± 9	73 ± 11	ns	ns	ns	P = 0·004	ns	ns

ns, statistically not significant.

Table 3 Systolic measurements of the left ventricle in 30 volunteers. Time I is before snuff intake, time II is 5 min after snuff intake, time III is 30 min after snuff intake and time IV is 30 min after snuff withdrawal.

Measurement $n = 30$	Time I	Time II	Time III	Time IV	I versus II	I versus III	I versus IV	II versus III	II versus IV	I II versus IV
LVEF (Simpson %)	63 ± 5	63 ± 5	64 ± 5	63 ± 5	ns	ns	ns	ns	ns	ns
MAM mean four sites (mm)	15·1 ± 1·7	15·1 ± 1·6	15·1 ± 1·6	15·3 ± 1·5	ns	ns	ns	ns	ns	ns
S mean four sites (cm s^{-1})	10·2 ± 1·6	10·1 ± 1·6	10·0 ± 1·6	10·0 ± 1·6	ns	ns	ns	ns	ns	ns
Septal S (cm s^{-1})	9·3 ± 1·1	9·1 ± 1·1	8·9 ± 1·3	8·8 ± 1·0	ns	ns	P = 0·02	ns	ns	ns
Lateral S (cm s^{-1})	10·8 ± 2·3	10·8 ± 2·4	10·8 ± 2·4	10·8 ± 2·3	ns	ns	ns	ns	ns	ns
Posterior S (cm s^{-1})	10·2 ± 1·6	10·2 ± 1·6	10·1 ± 1·3	10·1 ± 1·5	ns	ns	ns	ns	ns	ns
Anterior S (cm s^{-1})	10·3 ± 2·0	10·2 ± 2·1	10·2 ± 2·2	10·3 ± 2·1	ns	ns	ns	ns	ns	ns
CC-DTI S mean four sites (cm s^{-1})	7·6 ± 1·3	7·6 ± 1·3	7·5 ± 1·3	7·5 ± 1·3	ns	ns	ns	ns	ns	ns
Septal CC-DTI S (cm s^{-1})	7·1 ± 0·8	7·1 ± 0·9	7·1 ± 1·1	6·8 ± 0·9	ns	ns	ns	ns	ns	ns
Lateral CC-DTI S (cm s^{-1})	7·7 ± 1·8	7·6 ± 2·0	7·7 ± 2·1	7·8 ± 1·9	ns	ns	ns	ns	ns	ns
Posterior CC-DTI S (cm s^{-1})	7·8 ± 1·3	7·8 ± 1·1	7·8 ± 1·1	7·5 ± 1·2	ns	ns	ns	ns	ns	ns
Anterior CC-DTI S (cm s^{-1})	7·9 ± 2·1	7·8 ± 1·9	7·5 ± 1·8	7·8 ± 2·3	ns	ns	ns	ns	ns	ns

ns, statistically not significant; LVEF, left ventricular ejection fraction; MAM, mitral annulus motion; S, systolic velocity in long axis direction obtained using pulsed wave Doppler tissue imaging; CC-DTI S, systolic velocity obtained using color-coded Doppler tissue imaging.

Table 4 Diastolic measurements of the left ventricle in 30 volunteers. Time I is before snuff intake, time II is 5 min after snuff intake, time III is 30 min after snuff intake and time IV is 30 min after snuff withdrawal.

Measurement $n = 30$	Time I	Time II	Time III	Time IV	I versus II	I versus III	I versus IV	II versus III	II versus IV	III versus IV
E/A (ratio)	2·11 ± 0·74	1·78 ± 0·57	1·79 ± 0·56	1·99 ± 0·63	P = 0·002	P<0·001	ns	ns	P = 0·005	P = 0·01
E (m s^{-1})	0·78 ± 0·18	0·76 ± 0·16	0·75 ± 0·16	0·76 ± 0·15	ns	ns	ns	ns	ns	ns
A (m s^{-1})[a]	0·41 ± 0·14	0·46 ± 0·12	0·45 ± 0·12	0·41 ± 0·12	P = 0·05	ns	ns	ns	P = 0·005	P = 0·02
DT (ms)[a]	181 ± 26	195 ± 30	193 ± 22	180 ± 24	ns	ns	ns	ns	P = 0·01	P = 0·04
IVRT (ms)	68 ± 11	74 ± 8	77 ± 11	70 ± 10	P = 0·005	P<0·001	ns	ns	P = 0·03	P = 0·006
é mean four sites (cm s^{-1})	14·5 ± 3·0	14·5 ± 3·1	14·4 ± 3·1	14·8 ± 2·9	ns	ns	ns	ns	ns	ns
á mean four sites (cm s^{-1})	8·0 ± 2·0	8·6 ± 2·1	8·4 ± 1·8	7·9 ± 1·9	P<0·001	P = 0·04	ns	ns	P = 0·001	P = 0·004
CC-DTI e mean four sites (cm s^{-1})[a]	11·4 ± 2·4	11·1 ± 2·5	11·2 ± 2·5	11·4 ± 2·5	ns	ns	ns	ns	ns	ns
CC-DTI a mean four sites (cm s^{-1})	5·4 ± 1·8	5·9 ± 1·8	5·8 ± 1·7	5·4 ± 1·7	P = 0·002	P = 0·02	ns	ns	P = 0·01	P = 0·007
E/é (ratio)	5·5 ± 1·2	5·4 ± 1·2	5·3 ± 1·0	5·2 ± 1·2	ns	ns	ns	ns	ns	ns

ns, statistically not significant; E, early diastolic velocity obtained using pulsed wave Doppler; A, atrial velocity obtained using pulsed wave Doppler; DT, deceleration time; IVRT, isovolumetric relaxation time; é, early diastolic velocity obtained using pulsed wave Doppler tissue imaging; á, atrial velocity obtained using pulsed wave Doppler tissue imaging; CC-DTI e, early diastolic velocity obtained using color-coded Doppler tissue imaging; CC-DTI a, atrial velocity obtained using color-coded Doppler tissue imaging.
[a]Shapiro–Wilks test was statistically significant, but the same conclusions could be drawn after the sensitivity test.

Right ventricular systolic function

The tricuspid annular motion (TAM) did not alter significantly using M-mode. When recording the systolic longitudinal velocities in the basal segment of the free lateral wall, a significant decrease was seen using color-coded DTI (CC-DTI S) (Table 5).

Right ventricular diastolic function

When looking at the diastolic function before and after snuff intake, one can see statistical significant differences in the tricuspid E/A ratio (E/A), tricuspid E-wave velocity (E) and the DT of the tricuspid inflow. One can also see statistical significant decrease in the peak early diastolic myocardial velocities measured with both pulse-wave DTI (é) and color-coded DTI (CC-DTI e) (Table 6).

Discussion

The main finding in the current study is the statistical significant decrease in E/A ratio and the delay in left- and right ventricular relaxation and thus a decrease in diastolic heart function. This study is to our knowledge the first to investigate this decrease in diastolic heart function caused by Swedish snuff. The significant decrease was induced immediately after the bag of snuff was put into the mouth. Some of the diastolic parameters returned to their initial state 30 min after snuff withdrawal and some parameters were still significantly altered even 30 min after snuff withdrawal compared to the initial recording. Almost every systolic parameter measured in the left and right ventricles did not show any significant change during the test. The findings from the pulse and blood pressure responses from the subjects were a bit more difficult to interpret than the systolic and diastolic heart parameters.

Pulse and blood pressure response

As shown in Table 2, the pulse did not alter significantly 5 or 30 min after snuff intake, comparing to before snuff intake. What did occur was that the pulse dropped significantly 30 min after snuff withdrawal comparing to the earlier three measurements. If the volunteers were a bit stressed before the

Table 5 Systolic measurements of the right ventricle in 30 volunteers. Time I is before snuff intake, time II is 5 min after snuff intake, time III is 30 min after snuff intake and time IV is 30 min after snuff withdrawal.

Measurement $n = 30$	Time I	Time II	Time III	Time IV	I versus II	I versus III	I versus IV	II versus III	II versus IV	III versus IV
TAM (mm)	24 ± 3	24 ± 3	24 ± 3	23 ± 3	ns	ns	ns	ns	ns	ns
S (cm s^{-1})	15·1 ± 1·9	15·0 ± 1·9	14·7 ± 1·9	14·7 ± 2·1	ns	ns	ns	ns	ns	ns
CC-DTI S (cm s^{-1})	11·8 ± 1·4	11·4 ± 1·5	11·4 ± 1·4	11·2 ± 1·6	P = 0·04	P = 0·04	P = 0·02	ns	ns	ns

ns, statistically not significant; TAM, tricuspid annulus motion; S, systolic velocity in long-axis direction obtained using pulsed wave Doppler tissue imaging; CC-DTI S, systolic velocity obtained using color-coded Doppler tissue imaging.

Table 6 Diastolic measurements of the right ventricle in 30 volunteers. Time I is before snuff intake, time II is 5 min after snuff intake, time III is 30 min after snuff intake and time IV is 30 min after snuff withdrawal.

Measurement $n = 30$	Time I	Time II	Time III	Time IV	I versus II	I versus III	I versus IV	II versus III	II versus IV	III versus IV
E/A (ratio)[a]	2·17 ± 0·68	1·77 ± 0·61	1·80 ± 0·58	2·03 ± 0·65	P<0·001	P<0·001	ns	ns	P = 0·008	P = 0·003
E (m s^{-1})	0·67 ± 0·14	0·58 ± 0·13	0·59 ± 0·13	0·61 ± 0·11	P<0·001	P = 0·006	P = 0·003	ns	ns	ns
A (m s^{-1})	0·33 ± 0·07	0·35 ± 0·08	0·35 ± 0·08	0·32 ± 0·09	ns	ns	ns	ns	ns	ns
DT (ms)[a]	157 ± 25	172 ± 26	183 ± 32	167 ± 25	P = 0·03	P<0·001	ns	ns	ns	P = 0·02
é (cm s^{-1})	17·1 ± 2·2	16·2 ± 2·8	16·3 ± 2·5	15·7 ± 2·9	P = 0·04	ns	P = 0·002	ns	ns	ns
á (cm s^{-1})	13·2 ± 3·9	13·4 ± 3·9	13·8 ± 4·6	13·0 ± 3·9	ns	ns	ns	ns	ns	ns
CC-DTI e (cm s^{-1})	12·3 ± 1·9	11·8 ± 2·2	11·6 ± 2·2	11·6 ± 2·2	P = 0·05	P = 0·02	P = 0·04	ns	ns	ns
CC-DTI a (cm s^{-1})	9·6 ± 2·9	9·7 ± 3·1	9·7 ± 3·2	9·6 ± 3·1	ns	ns	ns	ns	ns	ns
E/é (ratio)	4·0 ± 0·8	3·7 ± 1·1	3·7 ± 0·8	3·9 ± 0·7	ns	ns	ns	ns	ns	ns

ns, statistically not significant; E, early diastolic velocity obtained using pulsed wave Doppler; A, atrial velocity obtained using pulsed wave Doppler; DT, deceleration time; é, early diastolic velocity obtained using pulsed wave Doppler tissue imaging; á, atrial velocity obtained using pulsed wave Doppler tissue imaging; CC-DTI e, early diastolic velocity obtained using color-coded Doppler tissue imaging; CC-DTI a, atrial velocity obtained using color-coded Doppler tissue imaging.

[a]Shapiro–Wilks test was statistically significant, but the same conclusions could be drawn after the sensitivity test.

examination could be one explanation. Maybe 10 min of rest was not enough for the subjects to achieve their real resting heart rate. These findings may depend on that the last measurements might have been the true resting heart rate of the subjects.

Also, the blood pressure did not increase immediately after snuff intake as reported in previous studies (Hergens *et al.*, 2008). Instead, it dropped significantly immediately after snuff intake and were normalized 30 min after intake. One earlier study show that people that had been using snuff within 2 h before the measurements were carried out had significantly higher pulse and blood pressure at rest than non-snuffers (Bolinder *et al.*, 1997). In the current study, all of the participants had been instructed not to use snuff or cigarettes for at least 5 h before the examination. Maybe this time interval was not enough. Other possible explanations are that nicotine absorption from snuff is highly affected by the pH-level in the oral cavity (Fant *et al.*, 1999). In our study, we had no control over the pH-levels in the participants and therefore we can't know how much of the nicotine in the bag of snuff that actually was delivered to the blood stream for each individual.

The findings in the study are somewhat difficult to interpret but they show that snuff intake affects the loading conditions.

Systolic function of the left and right ventricles

The systolic parameters measured in the left and right ventricles in the subjects did mostly not alter significantly during the study. MAM and TAM remained unaltered during snuff usage and these findings are in agreement with the previous studies published regarding heart function and cigarette smoking (Alam *et al.*, 2002; Ilgenli & Akpinar, 2007; Barutcu *et al.*, 2008). LVEF also remained unaltered during the test. Although Giacomin *et al.* (2008) reported a hyperdynamic response of the right ventricular systolic function in patients smoking one cigarette, this hyperdynamic response of the systolic right ventricular function was not seen in the current study. What did occur was a significant decrease in the longitudinal systolic annular velocity in the free lateral wall of the right ventricle using CC-DTI. However, this significant decrease was not seen using PW-DTI and seem therefore to be of minor importance.

In the left ventricle, a significant decrease in the mitral annular longitudinal systolic velocities was seen only using PW-DTI in the septal wall. All the other sites (lateral, inferior and anterior walls) remained unaltered and therefore this decrease may be seen as random.

However, there are previous studies (Yip *et al.*, 2002a,b) showing that isolated diastolic dysfunction is very uncommon and that systolic parameters are affected in patients with diastolic dysfunction. They present that the systolic longitudinal velocities in the myocardium are decreased in patients with different types of diastolic dysfunction although the ejection fraction is preserved.

Diastolic function of the left and right ventricles

Previous studies (Alam *et al.*, 2002; Karakaya *et al.*, 2006; Gulel *et al.*, 2007; Ilgenli & Akpinar, 2007; Barutcu *et al.*, 2008; Ciftci *et al.*, 2008; Giacomin *et al.*, 2008) show that cigarette smoking induces a significant decrease in left and right ventricular diastolic functions. Similar findings were revealed in the current study on snuff users, indicating that also snuff is capable to induce immediately negative effects of the filling ability in the heart. The significant decrease in diastolic function was induced almost immediately after the bag of snuff was put into the mouth and was constant even 30 min after the bag had been in the mouth. As in previous studies on smoking (Alam *et al.*, 2002; Karakaya *et al.*, 2006; Gulel *et al.*, 2007; Ilgenli & Akpinar, 2007; Barutcu *et al.*, 2008; Ciftci *et al.*, 2008; Giacomin *et al.*, 2008), the main alteration in this study on Swedish snuff was the decrease in E/A ratio but also a delay of relaxation and alterations of the relaxation velocities in the myocardium.

In the left ventricle, the decrease in E/A ratio was seen owing to a significant increase in atrial contraction (A-wave). Also, a small drop in E-wave velocity through the mitral valve was seen, which contributed to the drop in E/A ratio, but this decrease was not statistically significant at the time. The opposite pattern was seen in the right ventricle where the drop in E/A ratio was seen owing to a significant drop in the E-wave velocity and a small increase in atrial contraction (A-wave), the later was however not statistically significant. The increase in A-wave at the left side is what you could expect when there is a delay of the relaxation, the pattern at the right side is more difficult to explain but it may be owing to the pressure differences between the two ventricles. However, the decrease in E/A ratio as well as the delay in relaxation of both the ventricles, are indicating that the hemodynamic changes are caused by administration of snuff resulting in a decrease in diastolic function.

Anyway, it must be highlighted that only two of the subjects in this study actually got impaired relaxation after the bag of snuff was put into the mouth. The greater part of the participants in the study was young adults and their decrease in for example E/A ratio was not pathological. Most subjects still had normal diastolic parameters after snuff administration even though the parameters altered towards the pattern of impaired relaxation in almost every subject.

The mechanisms behind these acute effects on the cardiovascular system caused by cigarette smoke and Swedish snuff is still not fully mapped. Earlier published studies (Alam *et al.*, 2002; Gulel *et al.*, 2007) discuss that the effects of cigarette smoke on the ventricular function might be caused owing to a combination of inhalation of nicotine, tare products, nitric oxide derived free radicals, carbon monoxide and numerous of other different chemicals. Dogan *et al.* (2011) show that even exposure to passive smoking gives an acute decrease in diastolic function and also points out that the mechanism behind this is complex and they suggest that carbon monoxide and increment in COHb levels may be amongst the effects causing this alterations.

If we compare the current study with the earlier ones with cigarettes and ventricular function we can easily see that snuff do not contain most of the chemical products that are present in cigarettes, despite this the same results were seen as in the earlier studies.

The main product, which is present in both snuff and cigarettes, is nicotine and it can be believed that this chemical substance is at least one of the major factors causing the acute effects on the cardiovascular system.

The health hazards of smoking are well established but the health hazards of snuff is not as well established. There are earlier studies conducted (Huhtasaari *et al.*, 1992; Bolinder *et al.*, 1994; Fant *et al.*, 1999; Hergens *et al.*, 2007), which indicates that snuff users have an increased risk of developing hypertension and cardiovascular disorders comparing to non-snuffers. However, there are also studies showing that snuff users do not have an increased risk of developing cardiovascular disorders comparing to non-snuffers (Asplund *et al.*, 2003; Wennberg *et al.*, 2007; Janzon & Hedblad, 2009). Hanna (2006) discuss nicotine effects on the cardiovascular system. Animal tests show that nicotine in plasma causes morphological abnormalities of the endothelium, which causes alteration of the vascular reactivity. Nicotine also induces degenerative and necrotic changes in the arterial walls and if the nicotine is delivered to the blood stream in combination with a high cholesterol diet it seems to aggravate the arterial damage. Animal studies have shown that nicotine has potential to affect the ion channels in the heart. For example, nicotine seems to block K^+ channels, which may lead to effects on the cardiac electrophysiology like alterations in the action potential. This nicotine effect may also contribute to induce cardiac arrhythmias (Hanna, 2006).

As previously discussed, Fant *et al.* (1999) show that snuff is capable of delivering high doses of nicotine to the bloodstream, even higher concentrations than obtained from cigarettes. They suggest that snuff should be considered as a public health burden in the same way as cigarette smoke does. However, Bolinder *et al.* (1997) do not report in their study that long-time use of smokeless tobacco significantly influence the physical fitness in well-trained middle-aged men but this does not actually say anything about the real heart function and the risk of developing cardiovascular disorders.

The diastolic heart function in long-term snuff users still remains unexplored. New studies are necessary to establish if long-term snuff users really have an increased risk of developing diastolic dysfunction in an earlier stage than non-snuffers.

Limitations

Most subjects in the study were young adults between 20 and 30 years old. Although, we had a few subjects that were older (up to 63 years old) and therefore the test group was a bit heterogeneous. Especially the diastolic heart parameters, alters normally with age. In this study, this led to that a few (five) parameters (especially the DT of the E-wave in the left and right ventricles) were not normally distributed within the test group because of the age differences and therefore differences in diastolic parameters. After a correction (sensitivity test) for the outliers in these specific parameters another ANOVA test was performed. In three parameters, the result from the second ANOVA test did not alter at all compared to the first ANOVA but in two parameters (DT in the left and right ventricles), the result from the second ANOVA test was slightly altered but it does not change the conclusion of the study.

Conclusions

The current study reveals that Swedish snuff causes a significant decrease in E/A ratio and a delay in ventricular relaxation in both the left and right ventricles and therefore a significant decrease in diastolic heart function during a short time. The systolic heart function in the subjects remained unaltered. This study is to our knowledge the first to investigate this decrease in diastolic heart function caused by snuff. The negative effect is an acute one but the decrease in diastolic heart function caused by snuff seems to be constant for a greater amount of time than the decrease caused by cigarette smoke. The mechanisms behind these alterations are probably very complex, but a combination of nicotine effects and loading conditions are most likely the main factors. However, what is still not investigated thoroughly enough is whether long-time snuff usage can cause a more permanent decrease in diastolic heart parameters and if snuffers will develop diastolic heart failure earlier than non-snuffers.

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