CLINICS

CLINICAL SCIENCE

Daily assessment of arterial distensibility in a pediatric population before and after smoking cessation

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OBJECTIVES: Cigarette smoking is an important modifiable cardiovascular risk factor associated with increased stiffness of the large arteries in adulthood. This study aimed to 1) evaluate arterial distensibility and echocardiographic measures in adolescent smokers before and after participation in a successful smoking cessation program and to 2) compare the findings obtained with data from a control population of healthy non-smokers.

METHODS: A total of 31 young smoking subjects (58.1% male; range: 11-18 years old; mean: 16.5±1.4 years old; mean tobacco consumption: 2.6±0.6 years) were examined before commencing and after taking part for at least 1 year in a smoking cessation program (mean: 1.4±0.3 years). Arterial stiffness was measured using the previously validated $QKd_{100\text{-}60}$ method. Twenty-four-hour ambulatory blood pressure monitoring and transthoracic echocardiography were also performed.

RESULTS: (Smokers before abuse cessation *vs.* smokers after abuse cessation) systolic blood pressure: $p<0.004$; diastolic blood pressure: $p<0.02$; mean blood pressure: $p<0.01$; $QKd_{100\text{-}60}$ value: 183±5 *vs.* 196±3 msec, $p<0.009$; p = ns for all echocardiographic parameters. (Smokers after abuse cessation *vs.* controls) systolic blood pressure: $p<0.01$; diastolic blood pressure: $p<0.03$; mean blood pressure: $p<0.02$; $QKd_{100\text{-}60}$ value: 196±3 *vs.* 203±2 msec, $p<0.04$; $p<0.02$, $p<0.01$, and $p<0.05$ for the interventricular septum, posterior wall, and left ventricular mass, respectively.

CONCLUSIONS: Despite successful participation in a smoking cessation program, arterial distensibility improved but did not normalize. This finding underlines the presence of the harmful effect of arterial rigidity in these individuals, despite their having quit smoking and their young ages, thus resulting in the subsequent need for a lengthy follow-up period.

KEYWORDS: QKd Interval; Atherosclerosis; Smoking; Adolescence; Prevention.

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INTRODUCTION

Cigarette smoking is a major preventable cause of cardiovascular disease. It has been estimated to underpin up to 30% of all deaths from coronary heart disease, with a strong dose-related risk. Moreover, smoking significantly increases the risk of ischemic stroke, peripheral vascular disease, cancer, chronic lung disease, and numerous other chronic diseases (1,2).

Generally speaking, while the adverse effects of smoking become manifest in the fourth to fifth decades of life, the majority of smokers (SMs) acquire the habit in their early or mid-teens (3).

SMs are at an increased risk of developing accelerated atherosclerosis, as indicated by previous findings of structural anomalies in the carotid and brachial arteries of adult chronic SMs (4-6).

Increased vascular oxidative stress has also been detected in the arteries of passive SMs, as revealed by impaired flow-mediated vasodilatation, an early marker of atherosclerosis (7). Furthermore, loss of the natural elasticity of the aorta could likewise be responsible for the higher blood pressure values registered in SMs (8). However, significant improvement in arterial distensibility has been demonstrated in a

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number of studies of adult former SMs after smoking cessation programs lasting from 6 months to 2 years (9-16).

However, all of the reports published to date on tobacco-induced diseases and the effects of smoking cessation have focused on adult patients. It therefore remains to be clarified whether these findings can be translated to adolescent SMs, who have a shorter history of tobacco use compared with adults.

The QKd interval is the time (measured in milliseconds) between the onset of depolarization on electrocardiography (Q) and detection of the last Korotkoff sound (K) at the brachial artery during cuff deflation, corresponding to the diastolic blood pressure (d). The clinical validation, reproducibility, and prognostic value of the QKd index in providing valuable information on arterial compliance have been established by several previously published studies conducted on subjects with either normal or high blood pressure. Before the age of 30 years old, the QKd index is related to height but not age (17-23). The QKd technique has previously been validated in comparison to pulse wave velocity (19). Previous studies in pediatric patients have been performed as well (24,25). Because this interval is inversely correlated with pulse wave velocity, QKd measurement provides valuable information on arterial distensibility, as it is calculated using an arterial segment including the ascending aorta and a portion of the subclavian and brachial arteries (20).

The present study aimed to 1) evaluate arterial compliance before and after smoking cessation in adolescent SMs, 2) compare data obtained after smoking cessation with those from a control group (C) of healthy non-SMs, and 3) evaluate the echocardiographic data of adolescent SMs before and after quitting smoking.

This study is believed to be the first to investigate the effects of smoking cessation on arterial stiffness in a cohort of adolescent subjects. Based on the findings of previous studies performed in adults to investigate the reduction (but not normalization) in vascular damage induced by smoking cessation, the authors investigated the possibility for adolescents to achieve goals that were not achieved in adults.

PATIENTS AND METHODS

Selection of study participants

Thirty-eight participants were initially enrolled, although only 31 were included in the statistical analysis due to the exclusion of seven young subjects who proved unable to quit smoking.

Accordingly, thirty-one pediatric subjects (18 males and 13 females) with the habit of smoking up to 1 pack-year (from 8 to 20 cigarettes/day) and aged between 11 and 18 years old (mean age: 16.5 ± 1.4 years) were included in the study. The mean duration of tobacco use was 2.6 ± 0.6 years. All of the subjects were examined at the time of enrollment (confirmation of at least 48 hours of abstinence from smoking was ascertained by dosing nicotine metabolites in the urine) and, subsequently, after having quit smoking for at least 1 year (mean: 1.4 ± 0.3 years). At the time of the second evaluation, abstinence from smoking was likewise ascertained by assessing the presence of nicotine metabolites in the urine. Furthermore, during the 1-year smoking cessation program, three additional urine controls were performed to confirm smoking cessation. Specifically, urinary levels of the nicotine metabolite cotinine were assessed (26). Cotinine levels <10 ng/mL were considered consistent with no active smoking.

At baseline and follow-up, all SMs were strictly followed for 24 hours by their parents to ascertain their abstinence from both caffeine-containing beverages and physical exercise, both of which are potentially capable of affecting the evaluation of arterial stiffness. No cases of alcohol intake or drug abuse or addiction were reported between the baseline and follow-up examinations.

The young participants in the study quit smoking with the aid of a psychosocial program (based on peer pressure, parents as role models, the health consequences of smoking, the cost of smoking, tips for quitting smoking, and responsible decision making) (27). In Italy, nicotine replacement therapy and varenicline have not been approved for use in patients younger than 18 years old (28).

SMs were compared with a C of 31 healthy subjects paired with regard to sex, age, height, and weight. The controls were healthy subjects visited for certification of eligibility in sports. The exclusion criteria were the same in the study population and controls, i.e., conditions that increase the pre-ejection period and conditions that might impair interpretation of the QKd interval (such as severe subvalvular aortic stenosis, hyperthyroidism, presence of a pacemaker, left bundle branch block, and atrial fibrillation) (20). Subjects suffering from diseases known to influence arterial compliance (e.g., diabetes or autoimmune pathologies) were also excluded from the study. In this regard, three subjects were not enrolled because they were suffering from diabetes.

Table 1 shows the main clinical characteristics of the 31 smoking subjects and the controls.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM), QKd interval measurement (at baseline and at the end of the study), 12-lead surface ECG (at baseline), and transthoracic echocardiography (at baseline and at the end of the study) were performed for each study participant. In the smoking group, none of the enrolled subjects exhibited arterial hypertension.

This case-control study commenced in January 2001 and was finished in March 2012, due to the objective difficulty in recruiting this type of young subject. All of the young patients' parents gave their informed written consent for the study, which was conducted according to the Helsinki Declaration.

QKd interval measurement

The authors performed 24-hour ABPM using the auscultatory mode, coupled with measurement of the QKd interval, to evaluate the rigidity of the large arteries. A microphone was located in the cuff on the brachial artery, and three electrodes were placed on the subject's chest to detect QRS complexes. The QKd interval was measured together with concomitant cardiac frequency and blood pressure values every 15 minutes over a 24-hour period (approximately 96 values for each subject). QKd interval variations were automatically detected by a monitoring device, using purpose-developed software (Dyasis Integra from Novacor, Rueil Malmaison, France). This index provides an estimate of arterial distensibility derived from the pulse wave velocity (29). The measurement of the latter is undoubtedly the oldest method available for use in estimating the rigidity of an arterial segment. The principle

Table 1 - Clinical characteristics at baseline.

	Chronic smoking subjects (n = 31)	Control group (n = 31)	Statistical significance (*p*-value)
Age (years)	16.5 ± 1.4	15.9 ± 1.6	ns
Male subjects	18	18	ns
Female subjects	13	13	ns
Height (cm)	167.7 ± 5.8	164.9 ± 6.4	ns
Weight (kg)	63.6 ± 3.8	65.2 ± 3.7	ns
Body mass index (kg/m^2)	22.7 ± 1.1	24.1 ± 0.9	ns
Systolic BP at rest (mmHg)	132.4 ± 2.9	115.9 ± 3.3	0.001
Diastolic BP at rest (mmHg)	80.2 ± 3.5	74.4 ± 3.0	0.02
Heart rate at rest	78.3 ± 7.4	62.6 ± 3.1	0.001

Clinical characteristics (mean values ± standard deviations) of the 31 chronic smokers, compared with those of the 31 healthy non-smokers in the control group.
Abbreviations: BP = blood pressure.

of this technique is fairly simple: the more rigid the artery is, the more quickly the vibration generated by the ventricular ejection transmitted by the arterial wall is. With regard to the previously reported strong inverse relationship between pulse wave velocity and the QKd index, any elevation of the former results in a shortening of pulse wave transmission time and, therefore, of the QKd interval. The QKd technique is therefore closely correlated with the measurement of pulse wave velocity, and it presents two major advantages: measurement is completely automatic, and it can be used to measure different blood pressure levels. It is the variations in this time according to blood pressure that render the technique valuable (30).

Application of the above device allowed us to calculate automatically the QKd $_{100–60}$ index, i.e., the value of QKd for a systolic blood pressure of 100 mmHg and a heart rate of 60 beats per minute, which was totally independent of blood pressure levels and heart rate. This in turn reduces the influence of pre-ejection time (linearly correlated to heart rate) and simplifies comparisons among subjects with different blood pressure levels (20). It is indeed an acknowledged fact that SMs are at risk of developing hypertension, even at young ages (31). Values of QKd $_{100-60}$ exceeding 200 msec were considered normal (18).

As movement and physical activity frequently result in invalid readings when using machines that rely on the detection of Korotkoff sounds with simultaneous ECG recording, our device was programmed to obtain additional readings if a likely erroneous reading was recorded. We followed the generally accepted rule that an ABPM recording was not acceptable if less than 85% of readings were suitable for use in analysis (32). Accordingly, 24-h ABPM was repeated in six of the 31 cases studied. The device we used was capable of detecting the supine/orthostatic position of the subjects. The latter aspect, together with analysis of heart rate variability, provided relatively certain confirmation that only ABPM data from SMs registered under relaxed bodily conditions were analyzed.

Electrocardiography and echocardiography

All of the study participants underwent 12-lead surface ECG. A transthoracic echocardiographic study was performed by the same trained physician before the evaluation of arterial compliance by measuring the QKd interval. Left ventricular mass was calculated using Devereux's formula and was indexed by height to the power of 2.7 (33).

Statistical analysis

The sample was tested for normality using the Shapiro-Wilk test.

The results obtained for the entire smoking population (n = 31), expressed as means ± standard deviations, were compared to those of the C (n = 31) using the non-parametric Mann-Whitney U test. Regarding the QKd index, no differences between the sexes were observed (34). QKd analysis was performed based on the reference values obtained in previous studies conducted on subjects with either normal or high blood pressure (34).

Relationships between the various parameters were studied by univariate analysis. Multiple stepwise linear regression analysis was not performed because of the small sample size. Values of $p<0.05$ were set as the minimum level of statistical significance throughout the study.

For all of the analyses, commercially available computer software (SPSS version 20.0, SPSS Inc., Chicago, Illinois, USA) was used.

RESULTS

The participants were divided into two groups (Table 2): a) smoking subjects prior to a successful smoking cessation program lasting at least 1 year and b) smoking subjects following a successful 1-year smoking cessation program. The first group displayed significant differences in 24-hour ABPM and heart rate values when compared with data obtained after the cessation program. The participants were further divided into two subgroups (Table 3): a) SMs after stopping smoking and b) controls. Even after the 1-year cessation program, young former SMs had higher BP values and higher heart rates when compared with the C.

The 24-h ABPM values were different in former SMs when compared with the C. Indeed, the nocturnal declines in diastolic blood pressure were normal in the majority of the C (66 ± 4 mmHg diurnal diastolic blood pressure *vs.* 58 ± 3 mmHg nocturnal diastolic blood pressure, $p = 0.04$) but were reduced in most former SMs (69 ± 3 mmHg diurnal diastolic blood pressure *vs.* 67 ± 2 mmHg nocturnal diastolic blood pressure, $p>0.05$). In the C, nocturnal declines in diastolic blood pressure were detected in thirty individuals (dipper cases), whereas a similar finding was observed in only two members of the 1-year smoking cessation group (non-dipper cases; $p<0.0001$). In contrast, the nocturnal declines in systolic blood pressure were normal in both previous SMs and the C (ex-SMs: 120 ± 6 mmHg diurnal systolic blood pressure *vs.* 106 ± 5 mmHg

Table 2 - Twenty-four-hour ambulatory blood pressure monitoring data (before and after smoking).

	Smoking Subjects (baseline) (n = 31)	Smoking Subjects (follow-up) (n = 31)	Statistical significance (*p*-value)
SBP 24 hours	128 ± 4	113 ± 5	0.004
DBP 24 hours	77 ± 7	68 ± 6	0.02
MAP 24 hours	111 ± 6	98 ± 5	0.01
Heart rate	65 ± 3	72 ± 4	0.05

Data from 24-hour ambulatory blood pressure monitoring (smokers before and after a 1-year smoking cessation program. Mean values ± standard deviations).
Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure.

nocturnal systolic blood pressure, $p = 0.0001$. C: 108 ± 6 mmHg diurnal systolic blood pressure *vs.* 100 ± 5 mmHg nocturnal systolic blood pressure, $p = 0.001$). The C consisted of 28 dipper cases for systolic blood pressure, and the smoking group consisted of 25 ($p > 0.05$).

Regarding the echocardiographic data (Table 4), significant inter-group differences were observed in left ventricular mass and septal and posterior wall thicknesses.

With regard to the QKd $_{100–60}$ index, the values obtained before and after quitting smoking significantly differed (183 ± 5 *vs.* 196 ± 3 msec; $p < 0.009$). Furthermore, a statistically significant difference was observed in the QKd $_{100–60}$ index subsequent to smoking cessation when compared with the control group (196 ± 3 *vs.* 203 ± 2 msec; $p < 0.04$).

Univariate analysis demonstrated significant relationships between the QKd interval and increased blood pressure values, interventricular septal wall thicknes, and left ventricular mass ($r = 0.51$, $p = 0.003$; $r = 0.47$, $p = 0.007$; $r = 0.49$, $p = 0.004$, respectively). No other significant relationships were found.

DISCUSSION

To the best of our knowledge, no other studies to date have been undertaken to evaluate the profiles of arterial stiffness in individuals who were children or adolescents at the time of tobacco use. The findings obtained in the present study confirm previous reports of increased rigidity, even at a very young age, of the large arteries in adult SMs following smoking cessation (9-16). Increased arterial stiffness could represent the predisposing cause of the higher 24-hour ABPM values in these subjects.

The majority of the former SMs in this study showed a lack of physiological nocturnal declines in their diastolic blood pressure values. This non-dipper pattern appears related to poorer health outcomes and organ damage (32).

Moreover, in the present study, we showed that arterial compliance was lower in adolescent SMs than in the C, even after a smoking cessation program lasting at least one year, with lower QKd values in these individuals than in the C, based upon pulse wave velocity measurement. The latter finding emphasizes early deterioration in the physical properties of the arteries in young SMs that persist after quitting smoking. In individuals without overt coronary artery disease, smoking accelerates arterial aging. This tobacco-induced damage slows after smoking cessation (35). Even light smoking (i.e., ≤15 cigarettes/day with ≤8 pack-years of smoking history) in young healthy individuals appears to impair vascular function, affecting the ability of the vascular bed to respond to increased demands, such as those manifested during physical exercise (36).

Previously, arterial distensibility in SMs (during active tobacco use or passive exposure to smoke or after quitting smoking) has been evaluated using indices capable of providing an evaluation only at the time of examination; conversely, the QKd interval technique provides a complete profile of circadian variations in pulse wave velocity (9,10,37). A 24-hour evaluation would be more appropriate than a single measurement in assessing arterial elasticity (38). The vascular damage induced by the two major compounds in cigarette smoke (nicotine and carbon monoxide) might be responsible for the increased arterial rigidity in these individuals. Specifically, nicotine acts preferentially on the large arteries through sympathetic stimulation and catecholamine release, thus antagonizing endothelial nitric oxide action and inducing vasoconstriction (39). Carbon monoxide acts on small arteries by producing carboxyhemoglobin (oxygen is removed from hemoglobin and is replaced with carbon monoxide), thus inducing tissue hypoxia and impairment of cellular metabolism at the endothelium). All of these actions set the stage for the build-up of atherosclerotic plaques (39).

In agreement with previous studies on hypertensive patients, a relationship was observed between the decrease in the QKd interval values and increased blood pressure values, confirming the well-established importance of blood pressure in arterial compliance (19,40). With regard to the cardiac repercussions of the reduction in arterial compliance, we found significant relationships between the QKd interval and the interventricular septal and posterior wall

Table 3 - Twenty-four-hour ambulatory blood pressure monitoring data (before smoking *vs.* controls).

	Smoking Subjects (baseline) (n = 31)	Control Group subjects (follow-up) (n = 31)	Statistical significance (*p*-value)
SBP 24 hours	113 ± 5	104 ± 6	0.01
DBP 24 hours	68 ± 2	62 ± 3	0.03
MAP 24 hours	98 ± 3	90 ± 4	0.02
Heart rate	72 ± 4	82 ± 5	0.04

Data from 24-hour ambulatory blood pressure monitoring (ex-smoking subjects *vs.* the control group. Mean values ± standard deviations).
Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure.

Table 4 - Echocardiographic data.

	Smoking Subjects (baseline) (n = 31)	Smoking Subjects (follow-up) (n = 31)	Control group (n = 31)
IVS (mm)	10.6 ± 0.9	10.3 ± 0.7 *	9.3 ± 0.6 **
PW (mm)	10.1 ± 0.7	9.9 ± 1.1 *	8.3 ± 1.3 ***
LVDD (mm)	45.5 ± 1.9	44.4 ± 1.7 *	46.1 ± 1.2 *
LVSD (mm)	30.6 ± 2.6	31.0 ± 2.7 *	30.5 ± 2.2 *
LVM index (g/m$^{2.7}$)	52.5 ± 5.5	50.0 ± 4.8 *	47.3 ± 3.3 ****

Statistical significance:
*ns
**0.02
***0.01
****<0.05
Echocardiographic findings (mean values ± standard deviations).
Abbreviations: IVS = interventricular septum; PW = posterior wall; LVDD = diastolic diameter of the left ventricle; LVSD = systolic diameter of the left ventricle; LVM = left ventricular mass.

thicknessesand left ventricular mass, similar to previous observations reported for essential hypertension (41).

In addition, the echocardiographic findings obtained in this study (SMs *vs.* the C) were in accordance with previous reports related to cardiac structural manifestations of smoking (increased wall thickness and/or cardiac mass) in animal models (42).

Resting heart rate analysis revealed a significantly higher cardiac frequency in SMs compared to the C, in accordance with previously published data (43). Indeed, it is acknowledged that SMs have an increased sympathetic tone (43). The unexpected higher heart rate in the C, as shown in Table 3, was most likely due to the involvement of these subjects in usual daily activities, likely also including light/moderate physical activity for a number of subjects, in contrast to the strict control of the SMs during ABP. SMs alone were controlled for 24 hours. However, as previously reported, the QKd $_{100\text{-}60}$ index is completely independent of blood pressure levels and heart rate.

The main limitations of this study included the small number of participants and the consequent problems encountered in implementing the study. These limitations might have been complicated further by the difficulty in recruiting this type of young subject (it took several years to complete the study). Moreover, a smoking cessation program lasting at least one year might be an insufficient period over which to evaluate the efficacy of smoking cessation. A carefully monitored lengthy follow-up study should be implemented, as previously reported in adulthood (likely from 2 to 10 years) (9,44). In this regard, a continuation of QKd monitoring over a longer period to investigate potential correlations with arterial calcium storage, which develops over time, could prove to be of particular interest.

Additionally, compliance in young subjects is particularly difficult, with several subjects resuming cigarette smoking (45). To overcome this issue partially, during the 1-year quitting smoking program, nicotine metabolites in the urine were assessed three times to verify abstinence from smoking. Furthermore, at the end of the smoking cessation program, a further urine control was performed. Although the behavioral or medical treatment to be prescribed for pediatric SMs remains far from consensus, the authors suggest that all available strategies be used to encourage and implement smoking cessation programs in these individuals. By so doing, the specific aim would focus on increasing long-term smoking cessation rates, preserving natural aortic elasticity as long as possible, and reducing the morbidity and mortality associated with cardiovascular disease (31,46). As an additional limitation, due to the objective difficulty in recruiting this type of subject, the study participants were representative of a rather heterogeneous group (with a wide age range and a smoking history that differed in years of regular smoking and cigarettes smoked per day). This difference might have resulted in a discrepancy in the degree of arterial distensibility among these individuals, thus potentially explaining the lack of significant differences in echocardiographic measurements obtained in SMs at baseline and follow-up. Finally, other factors potentially contributing to the reduction in arterial compliance in SMs should be considered (e.g., elevated levels of plasma renin, catecholamines, and other endogenous vasoactive compounds and a family history of hypertension) (44).

In conclusion, the data obtained in this study demonstrated that SMs displayed early increased arterial stiffness (demonstrated by the changes captured using the QKd test) even in adolescence, regardless of the completion of a tobacco-use cessation program.

AUTHOR CONTRIBUTIONS

Bassareo PP and Fanos V conceived and designed the study, analyzed and interpreted the data, and prepared the manuscript. Bassareo PP and Crisafulli A performed the experiment and critically revised the manuscript. Crisafulli A participated in patient enrollment. Mercuro G critically revised the final manuscript version.

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