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

Pier Paolo Bassareo, I Vassilios Fanos, II Antonio Crisafulli, III Giuseppe Mercuro

I University of Cagliari, Department of Medical Sciences “M. Aresu”, Unit of Cardiology and Angiology, Cagliari, Italy. II University of Cagliari, Department of Surgery, Section of Neonatal Intensive Care Unit and Puericulture, Cagliari, Italy. III University of Cagliari, Department of Medical Sciences “M. Aresu”, Sport Physiology Laboratory, Cagliari, Italy.

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 100-60 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 < 0.01; QKd 100-60 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 100-60 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.
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
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 ± 5 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 diurnal systolic blood pressure, p = 0.002). 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/m²)| 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.
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.

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.
thicknesses and 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 QKd100-60 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 adult SMs (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.

### A U T H O R  C O N T R I B U T I O N S

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.

### R E F E R E N C E S

1. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. Circulation. 1997;96(9):3243-47.
2. Nelson DE, Kirkendall RS, Lawton RL, Chrismon JH, Merritt RK, Arday DA, et al. Surveillance for smoking-attributable mortality and years of potential life lost, by state—United States, 1990. MMWR CDC Surveill Summ. 1994;43(1):1-8.
3. Gupta R, Miera A, Vikram NK, Kondal D, Gupta SS, Agrawal A, et al. Younger age of escalation of cardiovascular risk factors in Asian Indian subjects. BMC Cardiovasc Disord. 2009;9:28, http://dx.doi.org/10.1186/1471-2261-9-28.
4. Mack WJ, Ottessen R, Selzer RH, Kwongfu H, Liu CR, Liu CH, et al. Passive and active exposure to tobacco smoke and subclinical carotid artery atherosclerosis. Circulation. 1998 (Suppl 1):I-582.
5. Tell GS, Polak JF, Ward BJ, Kittner SJ, Savage Pj, Robbins J. Relation of smoking with carotid artery wall thickness and stenosis in older adults.

---

### 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/m²²)                    | 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.
Arterial distensibility in former adolescent smokers

DeBon M, Klesges RC. Adolescents' perceptions about smoking prevention: a comparison of the programmes of the American Lung Association and the Tobacco Institute. Tob Control. 1996;5(1):19-25, http://dx.doi.org/10.1136/tc.5.1.19.

Goode P, Klesges RC. Adolescents' perceptions about smoking prevention: a comparison of the programmes of the American Lung Association and the Tobacco Institute. Tob Control. 1996;5(1):19-25, http://dx.doi.org/10.1136/tc.5.1.19.

Arterial distensibility in former adolescent smokers

Sobieray DM, White WB, Baker WL. Cardiovascular effects of pharmacological therapies for smoking cessation. J Am Soc Hypertens. 2013;7(1):61-7, http://dx.doi.org/10.1016/j.jash.2012.11.003.

Gómez-Marcos MA, Reñico-Rodríguez J, Fatimo-Alonso MC, Gómez-Sánchez L, Aguado-Conde C, Gómez-Sánchez M, et al. Ambulatory arterial stiffness indices and target organ damage in hypertension. BMC Cardiovasc Disord. 2012;12, http://dx.doi.org/10.1186/1471-2261-12-1.

Gosse P, Bemurat L, Mas D, Lemetayer P, Clementy J. Ambulatory measurement of the QKD interval normalized to heart rate and systolic blood pressure to assess arterial distensibility - value of QKD100-60. Blood Press Monit. 2001;6(2):85-9, http://dx.doi.org/10.1016/S0735-1097(01)00004-0.

Strong WB, Deckelbaum RJ, Gidding SS, Kavey RE, Washington R, Wilmore JH, et al. Integrated cardiovascular health promotion in childhood. A statement for health professionals from the Sub-committee on Atherosclerosis and Hypertension in Childhood of the Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 1992;85(4):1638-50.

Owen E, Coats A, Owens P, Petrie J, Padfield PL, Littler WA, et al. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British hypertension society. Br Med J. 2000;320(7242):1128-34, http://dx.doi.org/10.1136/bmj.320.7242.1128.

de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitis, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol. 1999;33(10):1251-60, http://dx.doi.org/10.1016/S0735-1097(99)00385-0.

Gosse P, Julienne V, Lemetayer P, Jarnier P, Clementy J. Ambulatory measurement of the timing of Korotkoff sounds in a group of normal subjects: influence of age and height. Am J Hypertens. 1999;12(2 Pt 1):231-5.

Jöckel KH, Lehmann N, Jaeger BR, Moebus S, Möhlenkamp S, Schmermund A, et al. Smoking cessation and subclinical atherosclerosis—results from the Heinz Nixdorf Recall Study. Atherosclerosis. 2009;203(1):221-7, http://dx.doi.org/10.1016/j.atherosclerosis.2008.05.041.

Doenan RJ, Scheffer P, Yu A, Egiziano G, Mutter A, Bacon S, et al. Altered arterial stiffness and subendocardial viability ratio in young healthy light smokers after acute exercise. PLoS One. 2011;6(10):e26151, http://dx.doi.org/10.1371/journal.pone.0026151.

Kallio J, Jokinen E, Hämäläinen M, Saarinen M, Volanen I, Kaitosaari T, et al. Decreased arterial elasticity in healthy 11-year-old children exposed to tobacco smoke. Pediatrics. 2009;123(6):e2667-73, http://dx.doi.org/10.1542/peds.2008-2659.

Kotsis V, Staboulis S, Karafillis I, Papakatiokas S, Rizes Z, Miyakos S, et al. Arterial stiffness and 24-h ambulatory blood pressure monitoring in young healthy volunteers: the early vascular ageing Aristotle University Thessaloniki Study (EVA-ARIS Study). Atherosclerosis. 2011;219(1):194-9, http://dx.doi.org/10.1016/j.atherosclerosis.2011.07.111.

Laviee A, Landini L, Vlodaver Z, et al. Pathologic Impulse Timing: Look at the Microcirculation! Curr Vasc Pharmacol. 2011;9(4):524-30.

Benetos A, Laurent S, Assmg RM, Lacolley P. Large artery stiffness in hypertension. J Hypertens Suppl. 1997;15(2):S89-97, http://dx.doi.org/10.1097/00004872-199715022-00009.

Gosse P, Gasparoux P, Ansbo P, Lemetayer P, Clementy J. Prognostic value of ambulatory measurement of the timing of Korotkoff sounds in elderly hypertensives: a pilot study. Am J Hypertens. 1997;10(5 Pt 1):552-6.

Azevedo PS, Minicucci MF, Matsubara BB, Matsubara LS, Duarte DR, Paiva SA, et al. Remodelling pattern and ventricular function in rats exposed to cigarette smoke. Arq Bras Cardiol. 2010;94(2):209-12.

Minami J, Ishimitsu T, Matsuoka H. Effects of smoking cessation on arterial stiffness. Br J Clin Pharmacol. 2006;61(6):767-73.

Esen AM, Barutcu I, Acar M, Degirmenci B, Kaya D, Turkmen M, et al. Ambulatory arterial stiffness—results from the Heinz Nixdorf Recall Study. Atherosclerosis. 2009;203(1):221-7, http://dx.doi.org/10.1016/j.atherosclerosis.2008.05.041.

Kallio J, Jokinen E, Hämäläinen M, Saarinen M, Volanen I, Kaitosaari T, et al. Decreased arterial elasticity in healthy 11-year-old children exposed to tobacco smoke. Pediatrics. 2009;123(6):e2667-73, http://dx.doi.org/10.1542/peds.2008-2659.

Kotsis V, Staboulis S, Karafillis I, Papakatiokas S, Rizes Z, Miyakos S, et al. Arterial stiffness and 24-h ambulatory blood pressure monitoring in young healthy volunteers: the early vascular ageing Aristotle University Thessaloniki Study (EVA-ARIS Study). Atherosclerosis. 2011;219(1):194-9, http://dx.doi.org/10.1016/j.atherosclerosis.2011.07.111.

Laviee A, Landini L, Vlodaver Z, et al. Pathologic Impulse Timing: Look at the Microcirculation! Curr Vasc Pharmacol. 2011;9(4):524-30.

Benetos A, Laurent S, Assmg RM, Lacolley P. Large artery stiffness in hypertension. J Hypertens Suppl. 1997;15(2):S89-97, http://dx.doi.org/10.1097/00004872-199715022-00009.

Gosse P, Gasparoux P, Ansbo P, Lemetayer P, Clementy J. Prognostic value of ambulatory measurement of the timing of Korotkoff sounds in elderly hypertensives: a pilot study. Am J Hypertens. 1997;10(5 Pt 1):552-6.

Azevedo PS, Minicucci MF, Matsubara BB, Matsubara LS, Duarte DR, Paiva SA, et al. Remodelling pattern and ventricular function in rats exposed to cigarette smoke. Arq Bras Cardiol. 2010;94(2):209-12.