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The effect of different extrinsic and intrinsic factors on the cardiovascular system

Doctoral (Ph.D.) Thesis

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PREFACE

Cardiovascular diseases including cerebrovascular diseases, ischemic heart diseases and peripheral vascular diseases are the leading causes of mortality worldwide being responsible for more than 1.8 million deaths annually, that is the 37% of all deaths in the European Union. Representing a far worse situation, the Hungarian cardiovascular mortality rate is 49% considering all age groups. The improving management of acute cardiovascular diseases (stroke, acute myocardial infarction) has led to the modification of mortality structure in recent decades: ischemic heart diseases are currently the most frequent cause of death among cardiovascular diseases. This disease group therefore places an outstanding economic burden of 210 billion Euros in the European Union. The management of atherosclerosis as a common underlying pathophysiological process of cardiovascular diseases including risk stratification, lifestyle changes and possible medical treatment is equally effective against cerebrovascular diseases, ischemic heart diseases and peripheral vascular diseases. The gold standard of cardiovascular risk stratification is the guideline of the European Society of Cardiology and the European Society of Hypertension, from which the guidelines introduced in 2007 and 2013 included arterial stiffness besides traditional risk factors. Arterial stiffness summarizes parameters describing the rigidity of large arteries including pulse wave velocity (PWV), augmentation index (AIX) and central systolic blood pressure (SBP_{ao}). Indirect, oscillometric values of these parameters represents a clear and apparent correlation with direct, invasively obtained values. My thesis consists of three independent studies in the field of cardiovascular risk stratification. The effect of relatively short (24-hour long) cessation of smoking on cardiovascular parameters was analysed in the first study. The aim of the second study was to determine the diurnal profile of arterial stiffness parameters in non-smokers, as well as to evaluate its potential variation of the diurnal profile in smokers. The third study aimed to assess the effect of AB0 blood groups on the cardiovascular risk.

INTRODUCTION

Cardiovascular morbidity and mortality

Cardiovascular diseases are responsible for more than 1.8 million deaths annually, that is the 37% of all deaths in the European Union. Reflecting the general trend, according to which death rates from ischemic heart disease and stroke are higher in Central and Eastern Europe than in Northern, Southern and Western Europe, the Hungarian situation is far worse. Figures 1 and 2 demonstrate an almost 8% difference between cardiovascular death rates among residents under 65 in Hungary (29.16%) and in the European Union (21.65%).

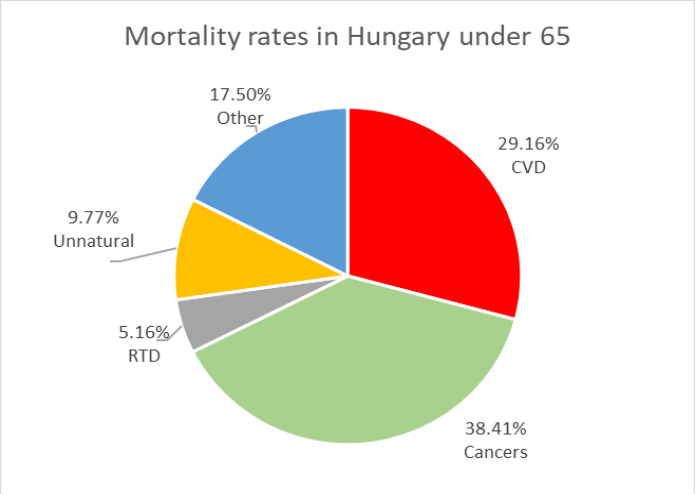


Figure 1. Mortality rates in Hungary under 65
Legend: CVD – cardiovascular diseases; RTD – respiratory tract diseases

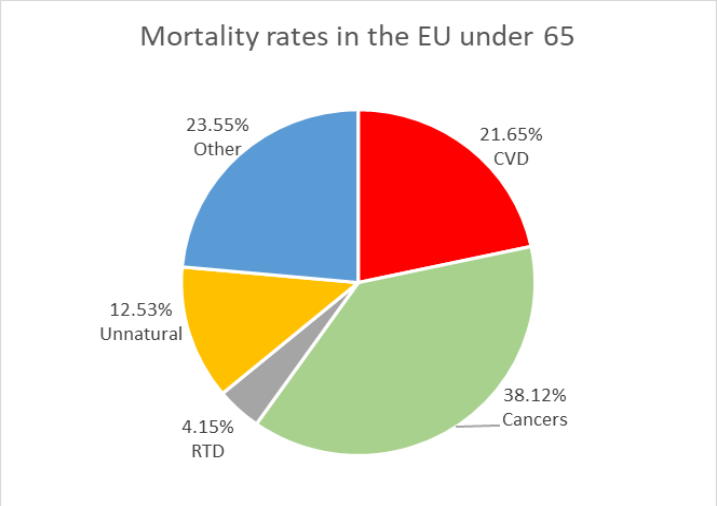


Figure 2. Mortality rates in the European Union under 65
Legend: CVD – cardiovascular diseases; RTD – respiratory tract diseases

Further subdivision of these groups according to sex (Figure 3 and 4) reveal that cardiovascular mortality is much higher among men in this age group (31.80% vs. 23.90% in Hungary; 24.10% vs. 16.85% in the European Union). Moreover, the regional difference is slightly more pronounced among men than among women (7.7% vs 7.05%, respectively).

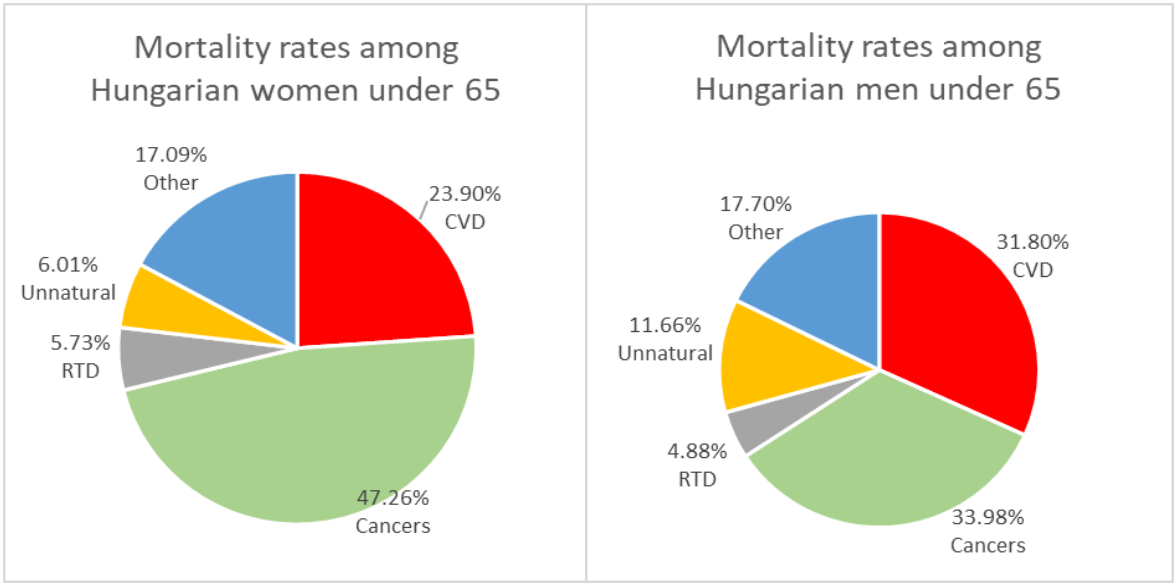


Figure 3. Mortality rates among Hungarian women and men under 65
Legend: CVD – cardiovascular diseases; RTD – respiratory tract diseases

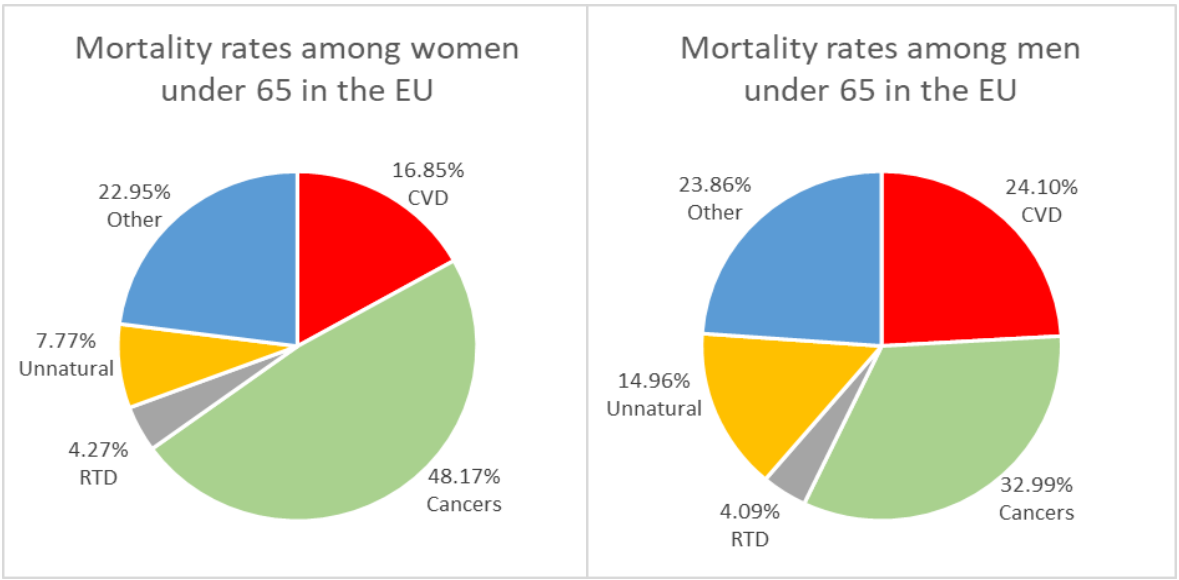


Figure 4. Mortality rates among women and men under 65 in the European Union
Legend: CVD – cardiovascular diseases; RTD – respiratory tract diseases

As Figure 5 and 6 represent, considering all age groups, cardiovascular mortality rate increases to 49.71% in Hungary and to 37.19% in the European Union. Furthermore, the difference between the aggregated cardiovascular mortality in Hungary and in the European Union increases as well to 12.52%.

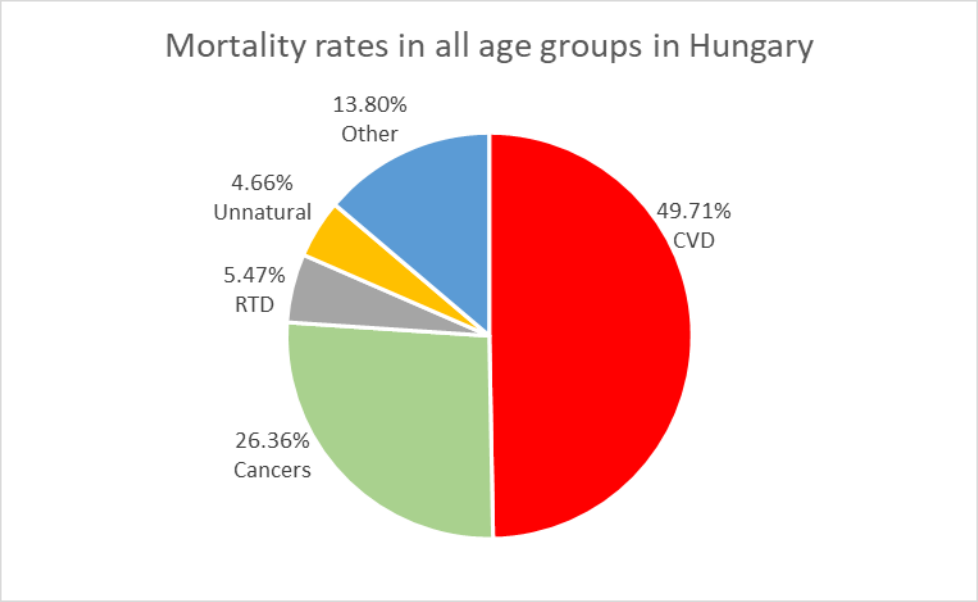


Figure 5. Mortality rates in all age groups in Hungary
Legend: CVD – cardiovascular diseases; RTD – respiratory tract diseases

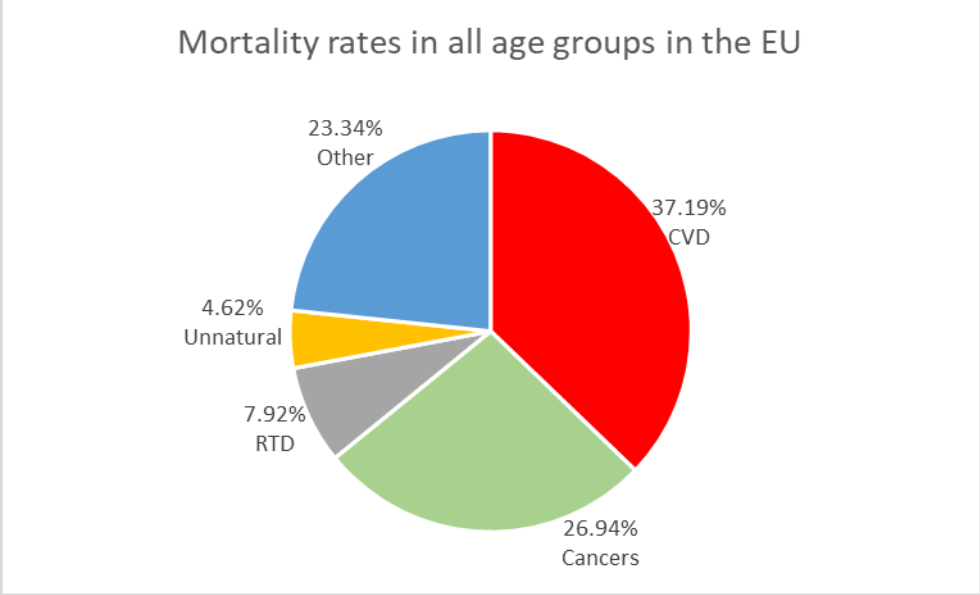


Figure 6. Mortality rates in all age groups in the European Union
Legend: CVD – cardiovascular diseases; RTD – respiratory tract diseases

As Figure 7 and 8 show, forming subgroups according to sex reveal that the tendency is opposite to that under 65, (partially) out of oestrogen effect cardiovascular mortality seems to be considerably higher among women than men (54.64% and 44.59% in Hungary; 40.19% and 34.15% in the European Union, respectively).

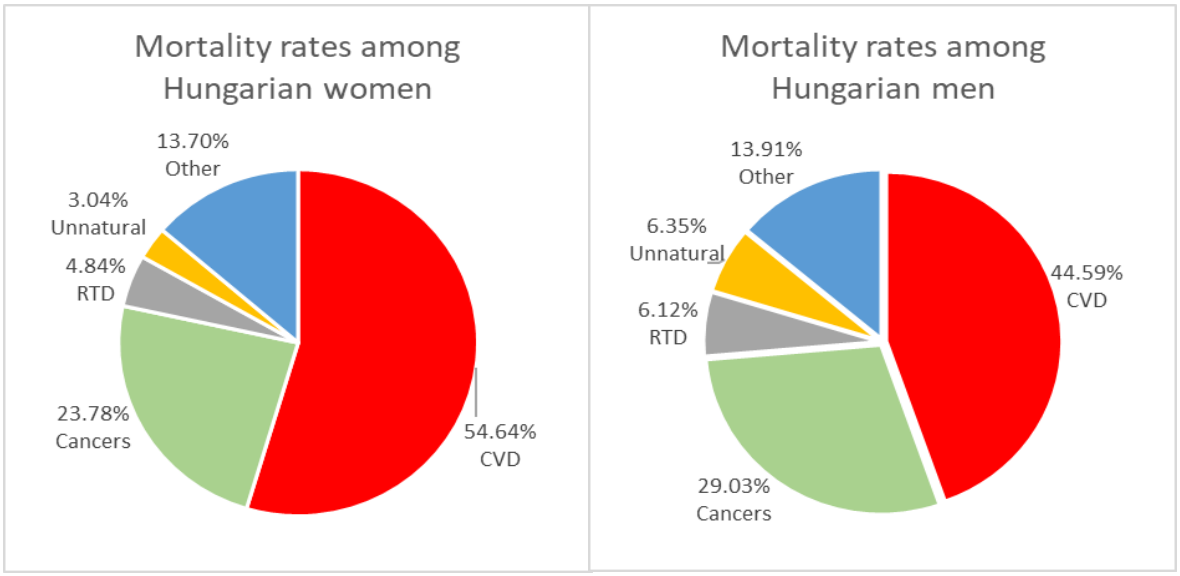


Figure 7. Mortality rates among Hungarian women and men
Legend: CVD – cardiovascular diseases; RTD – respiratpory tract diseases

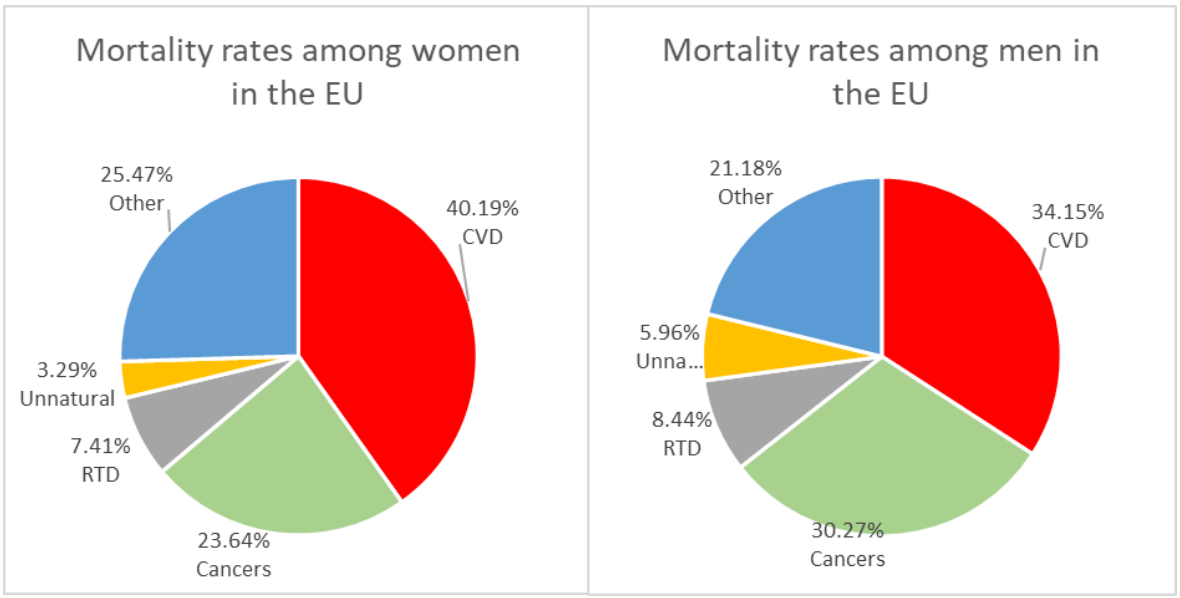


Figure 8. Mortality rates among women and men in the European Union
Legend: CVD – cardiovascular diseases; RTD – respiratory tract diseases

Nevertheless, it should be pointed out that the prevalence of cardiovascular diseases is also high. In Hungary, 555 656 males and 653 088 females lived with cardiovascular disease in 2015 accounting for an age-standardized prevalence rate for 100 000 individuals of 8 500 among men and 6552 among women. Whereas in the European Union, 24 297 499 males and 24 571 804 females lived with cardiovascular disease in the same year accounting for an age-standardised prevalence rate for 100 000 population of 6 308 among men and 4 021 among women. Thus, the apparent reversal of cardiovascular morbidity and mortality rates after menopause appears rather to be an equalization between the two genders [1].

On average, approximately 15 000 people are diagnosed yearly in Hungary with acute myocardial infarction, that has a 1-year mortality of 20-25%. The annual number of patients diagnosed with acute myocardial infarction has not changed considerably in recent years. Nonetheless, the number of patients dying from acute myocardial infarction has decreased sharply between 1993 and 2004 from 15 000 to 5872 and it has been stagnating since then [2]. Additionally, the mortality structure of cardiovascular diseases has also substantially changed, whereas vast majority of cardiovascular deaths occurred due to myocardial infarction and cerebrovascular diseases, nowadays chronic ischemic heart disease causing heart failure leads most frequently to death [1].

Beside cardiovascular deaths, the presented prevalence and mortality of cardiovascular diseases causes an outstanding economic burden. Overall, cardiovascular diseases are estimated to cost the EU economy €210 billion a year. This total cost – representing a greater economic burden than that of all other diseases – can be distributed as follows: approximately 53% (€111 billion) is due to healthcare costs, 26% (€54 billion) is due to productivity losses and 21% (€45) to the informal care of people with CVD. [1]

Cardiovascular risk stratification

The above-mentioned alarming morbidity and mortality data makes cardiovascular prevention particularly important. Beside well-known risk factors including hypertension, diabetes mellitus, dyslipidaemia, physical inactivity, unhealthy diet, obesity, smoking and alcohol consumption, recent studies revealed further risk factors, such as certain genetic disorders, increased blood viscosity, increased fibrinogen concentration, homocysteine accumulation and increased C-reactive protein (CRP) value for developing myocardial

infarction, stroke or peripheral vascular disease. Due to their common origin, namely atherosclerosis, preventive measures against any cardiovascular disease reduce the incidence of all other cardiovascular diseases, as well [3]. The 2007 and 2013 European Society of Cardiology/European Society of Hypertension guidelines for the management of arterial hypertension included the evaluation of arterial stiffness for evaluating both organ damage and cardiovascular risk [4, 5].

Arterial stiffness

Arterial stiffness characterized by aortic pulse wave velocity (PWV_{ao}), augmentation index (Aix) and central systolic blood pressure (SBP_{ao}) describes the rigidity of large arteries. Stiffening in the central arterial axis significantly contributes to the development of cardiovascular diseases, moreover, it is positively associated with systolic hypertension [6], coronary artery disease [7, 8], stroke [7], heart failure [9] and atrial fibrillation [10, 11]. Its importance was also highlighted in patients with end-stage renal disease [12-14], coronary artery disease [15-16], diabetes [17] and in apparently healthy population [18].

However, as the direct measurement of the above-mentioned stiffness parameters is time-consuming, requires trained professionals and does not allow the parallel determination of all parameters, their routine clinical application only became widespread after the introduction of indirect methods. Cziráki et al. performed the invasive validation of an oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity [19]. A study comparing Arteriograph to tonometric and piezo-electronic methods found the correlation of PWV obtained with Arteriograph, SphygmoCor and Complior highly significant, while variability and reproducibility for PWV appeared to be the best for Arteriograph [20]. Another study with highly similar method found that differences in pulse wave velocity obtained with different devices resulted primarily from the various methods used to measure travelled distance [21]. However, a third study analysing the same methods established that the techniques are closely related, the limits of agreement were wide, though, so they are not interchangeable [22].

Measurement principles of the Arteriograph

In the Arteriograph, an upper arm cuff functions as sensor pressurized at least 35 mmHg over the actual systolic pressure creating a small diaphragm at the level of the upper edge

of the overpressurized cuff. As the central pressure changes, early (direct) systolic wave (P_1), late (reflected) systolic wave (P_2) and diastolic wave(s) (P_3) reach this dedicated point causing a beat on the membrane and a small volume/pressure change in the cuff. These suprasystolic pressure changes are recorded by a high-fidelity pressure sensor. Conduit arteries including subclavian, axillary and brachial arteries transfer central pressure changes to the edge-position sensor. By stop-flow condition and occluded artery the local influence of brachial artery wall characteristics is practically eliminated, as the arterial wall remains immobile.

At each measurement, the device measures the actual systolic and diastolic blood pressure oscillometrically, then the cuff is decompressed. Afterwards, the cuff is inflated again, first to the point of actual diastolic pressure, then to the suprasystolic pressure (systolic pressure +35 mmHg) and records signals for 8 s (optionally up to 10 s). Data analysis is performed by the software designed for this purpose (version 1.10.0.1). Augmentation index is determined according to the following formula:

$$Aix\ (\%) = \frac{P_2 - P_1}{PP}\ x\ 100$$

where P_1 is the amplitude of the direct (first) wave, P_2 is the amplitude of the reflected (late) wave and PP is the pulse pressure.

The ejected direct (first systolic) pulse wave is reflected mainly from the aortic bifurcation allowing the determination of pulse wave velocity. Return time (RT) is calculated on the basis of the time interval between the peaks of the direct (first) and the reflected (late) systolic wave. Aortic length is estimated based on the distance between the sternal notch and the upper edge of the pubic bone (jugulum-symphisis distance) as it provides the nearest value of the true aortic length [23]. Pulse wave velocity was calculated according to the following formula:

$$PWV_{ao}(\frac{m}{s}) = \frac{Jug - Sy\ (m)}{RT/_2\ (s)}$$

where PWV_{ao} is the pulse wave velocity, Jug-Sy is the jugulum-symphisis distance and RT is the return time.

Central blood pressure was calculated based on the relationship between brachial and central systolic blood pressure on the basis of the late systolic wave amplitude. The blood pressure measuring algorithm of Arteriograph has been validated [24].

NOVEL ASPECTS OF DIFFERENCES IN ARTERIAL STIFFNESS PARAMETERS DURING SHORT ABSTINENT PERIOD IN SMOKERS VS. NON-SMOKERS

Introduction

It has long been recognized that tobacco smoking has great impact on morbidity and mortality. According to an indirect estimation from national statistics in developed countries alone, the number of annual tobacco-attributable deaths increased from 0.9 million in 1965 to 2.1 million in 1995. More than half of these deaths occurred between the age of 35 and 69 leading to an average loss of approximately 23 years of life expectancy in this age group [25]. Despite declines, tobacco smoking remained the leading risk factor for disease burden in North America and Western Europe [26]. The smoking-attributable mortality fraction for men in 2009 was 19% in England &Wales, 22% in Denmark and 25% in the Netherlands. According to the estimation of Stoeldraijer and colleagues, by 2050 a decline to 6, 12 and 14%, respectively, is foreseen., whereas the smoking-attributable mortality fraction by women peaked at 14% in 2008 in England & Wales and is expected to peak at 22% in 2028 in Denmark and at 23% in 2033 in the Netherlands. By 2050, a decline to 9, 17 and 19%, respectively, is foreseen [27]. Approximately 30-40% of smoking-related deaths are due to cardiovascular diseases [28].

Out of the numerous tobacco smoke compounds nicotine, carbon monoxide and oxidant gases are thought to be the main constituents to cause cardiovascular diseases. Nicotine is a potent gangliotic and central nervous system stimulant. Nicotine exerts its effects via sympathetic neural stimulation leading to significant hemodynamic changes including an increased heart rate, blood pressure, myocardial contractility and cardiac output leading to an increase in oxygen demand [29, 30]. The increase of heart rate can be observed both acutely as well as throughout the day with regular dosing [31, 32]. Binding to haemoglobin, reducing the amount of haemoglobin available to carry oxygen and impeding oxygen release from haemoglobin, carbon monoxide has been proven to reduce exercise tolerance in patients with angina pectoris, intermittent claudication and chronic obstructive lung

disease [33]. Carbon monoxide exposure has resulted in a greater degree of exercise-induced ventricular dysfunction and increased number and complexity of ventricular arrhythmias during exercise in patients with obstructive coronary disease [34]. Relative hypoxaemia due to chronic carbon monoxide exposure leads to an elevated red blood cell mass that is thought to contribute to increased blood viscosity and hypercoagulable state [35]. Exposure to oxidizing chemicals including oxides of nitrogen and different free radicals is associated with depletion of endogenous levels of antioxidants [36] and elevated lipid peroxidation products in the urine and plasma [37]. Oxidative stress is believed to contribute to numerous potential mechanisms of cardiovascular disease development including inflammation, endothelial dysfunction, lipid abnormalities and platelet activation [38]. Polycyclic aromatic hydrocarbons were reported to accelerate atherosclerosis in animal experimental models [39, 40].

The hemodynamic effects of tobacco smoking mediated primarily by nicotine include increased resting blood pressure, resting heart rate and myocardial contractility resulting in an increase in cardiac output and myocardial work [30]. As reviewed by Czernin and Waldherr, this increased myocardial work is associated with an increased coronary blood flow by up to 40% in healthy individuals [41]. Nevertheless, as cigarette smoking causes endothelial injury and dysfunction in both peripheral and coronary sites including reduced nitric oxide release [41, 42], impaired vasodilatory reserve, prothrombic state, increased neutrophil and monocyte adhesion to blood vessels and promotion of inflammation [42], the increase in coronary blood flow is less than expected based on the level of myocardial work in the absence of nicotine. Moreover, in the presence of coronary artery disease smoking increases coronary vascular resistance [43] and decreases coronary blood flow [44]. Cigarette smoking during coronary angiography has been observed to acutely trigger coronary vasospasm [45], whereas cigarette smoking is associated with poorer response to medication against vasospastic angina [46].

The hemodynamic effects of nicotine are hard to be established during exercise. Although heart rate and VO_{2max} appeared not to be modified at maximal exercise [47]; heart rate [47], blood pressure [48], cardiac output [47], systemic vascular resistance [49], myocardial oxygen consumption [49] and myocardial blood flow [49, 50] were markedly higher at submaximal levels. Nicotine was also found to enhance the increase in myocardial oxygen

consumption during heart pacing [50], moreover, due to endothelial dysfunction triggered by nicotine paradoxical coronary vasoconstriction can occur during exercise [51]. Exercise induced splanchnic vasoconstriction and subsequent decrease in blood flow is capable of impairing hepatic nicotine clearance, thus prolonging nicotine effect [47].

Several studies have confirmed that arterial stiffness increases acutely after cigarette smoking as measured by augmentation index (AIX), carotid-femoral pulse wave velocity (cfPWV), brachial-radial pulse wave velocity (brPWV) or carotid-radial pulse wave velocity (crPWV) [52, 53]. Kim et al. reported that at baseline, the brachial-ankle pulse wave velocity (baPWV) was not significantly different between smokers and non-smokers, but it was significantly higher in chronic smokers 5 minutes after cigarette smoking and remained higher for 30 minutes [54]. According to a systematic review on 39 relevant studies [55], more studies reported significantly higher aortic or brachial PWV, as well as AIX in chronic smokers than non-smokers. However, three different studies found no significant correlation between smoking status and cfPWV [55].

The importance of parameters describing arterial stiffness including pulse wave velocity, aortic augmentation index and central systolic blood pressure (SBPao) has been confirmed on patients with coronary artery disease [15] and hypertension [8, 56], as well as in apparently healthy population [18] and young sportsmen [57]. Thus, the evaluation of arterial stiffness was included in the 2007 and 2013 European Society of Cardiology / European Society of Hypertension guidelines for the management of arterial hypertension to evaluate both organ damage and cardiovascular risk [4, 5].

The acute and chronic effects of smoking on blood pressure and heart rate are well described by previous studies [58-60]. Nevertheless, its effect on arterial stiffness has only been partially evaluated in a systematic literature review paper [55]. Although several studies discuss the effects of smoking cessation on arterial stiffness, the chronic effects of smoking cessation (60 weeks, 6 months) were solely analysed. Similarly, previous studies used single measurements of stiffness values and were not self-controlled. Previous studies showed that smoking elicits constriction of resistance arteries and lead to an increase in systemic blood pressure [61]. Thus, we hypothesized that arterial stiffness values change significantly in the first 24 hours after smoking cessation due to the lack of vasoconstrictor effect of smoking [61]. Hence, our aim was to determine the effects of short-term smoking

cessation on arterial stiffness via a continuous measurement method with the exclusion of individual variables.

Materials and methods

In the first phase of our study, ten healthy light smoker (smoking a maximum of 10 cigarettes/day) volunteers were examined for 48 hours with a non-invasive ambulatory oscillometric device (Arteriograph 24 distributed by Tensiomed Kft Budapest, Hungary) between 1st April 2015 and 31st December 2015. The volunteers were ordered to abstain from cigarette smoking during the first 24 hours and were allowed to smoke during the second 24 hours. Inclusion criterion was smoking of at least 10 cigarettes during the second day. Day and night periods were adjusted individually; brachial systolic and diastolic blood pressure (DBP), heart rate and arterial pulse pressure waveform were measured, aortic systolic blood pressure (SBP), aortic augmentation index, brachial augmentation index and aortic pulse wave velocity were derived, whereas pulse pressure and mean arterial pressure were calculated in every 20 minutes during waking and in every 40 minutes during sleeping hours.

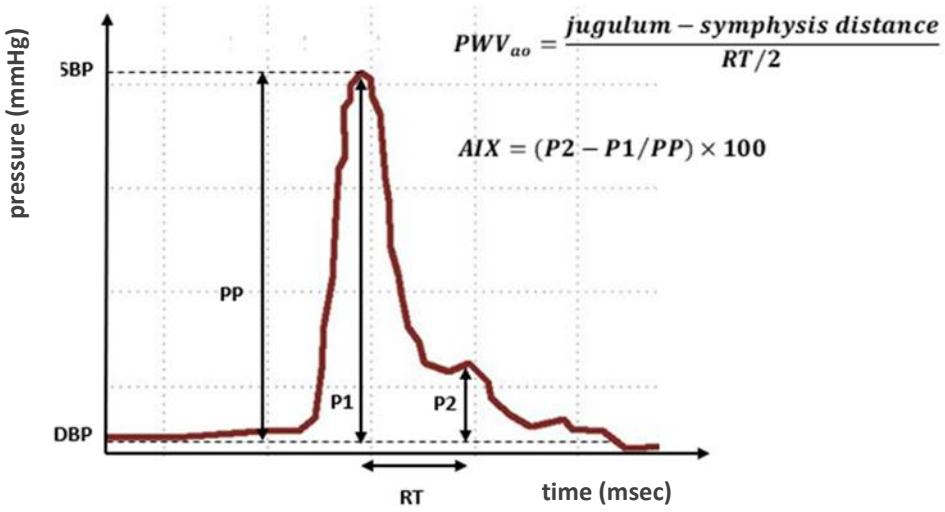


Figure 9. Calculation methods of pulse wave value and augmentation index from the pulse pressure waveform

P1 - Amplitude of the forward pressure waveform minus diastolic blood pressure value; P2 - Amplitude of the backward pressure waveform minus diastolic blood pressure value; RT - Return time; SBP - systolic blood pressure; DBP - diastolic blood pressure; PP - pulse pressure

As demonstrated in Figure 9, augmentation index was calculated as a difference of the reflected (second, backward, P2) and ejected (first, forward, P1) wave of the central pulse pressure waveform expressed as a percentage of pulse pressure. Pulse wave velocity was calculated as the jugulum-symphysis distance divided by the half of the return time.

In the second phase of the study, ten healthy, non-smoker, age-matched and BMI-matched volunteers were examined for 24 hours with the same method between 1st July 2017 and 31st December 2017. Informed consent was obtained from all volunteers prior to the examinations.

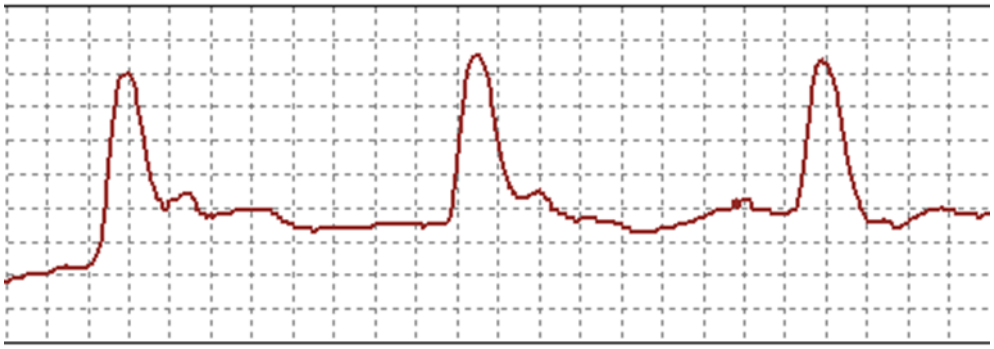
All participants abstained from alcohol-containing beverages and physical exertion outside usual daily activities. Exclusion criteria included any chronic disease that may affect cardiovascular function (e.g. chronic kidney disease, congenital heart defect or hypertension) and regular alcohol or drug consumption.

Each dataset was individually controlled, and invalid data were eliminated resulting in an average of 46 remaining values per day per parameter. Regarding missing data, only missing completely at random type occurred during the study, these data were omitted from further statistical analysis. Socio-demographic and statistical analysis was performed with IBM SPSS Statistics v22.0. The sample was tested for normality using the one-sample Kolmogorov-Smirnov test. The results obtained from the light smoker group during the smoking and non-smoking days, expressed as means ± standard deviations were compared to each other using the paired-sample T-test. The results of the control group and the light smoker group were compared to each other with the independent samples T-test.

Results

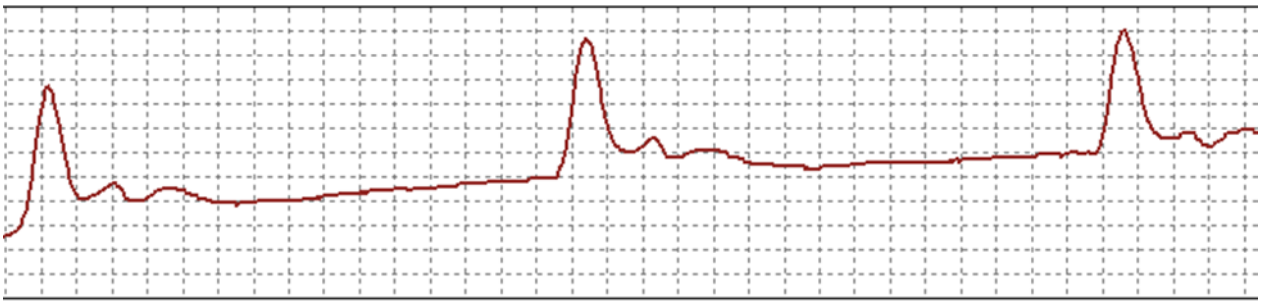
Mean age was 29.00±8.78 years in the test group and 28.90±10.72 years in the control group. Mean BMI was 22.89±3.42 in the test group and 22.14±2.33 in the control group. Neither in age ($p=0.98$) nor in body mass index (BMI, $p=0.57$), was statistical difference found among the two groups. The test group consisted of seven men and three women, while the control group consisted of four men and six women.

Figures 10-12 demonstrate a representative pulse pressure waveform of a negative control, a smoking person on the non-smoking day and a smoking person on the smoking day, respectively.



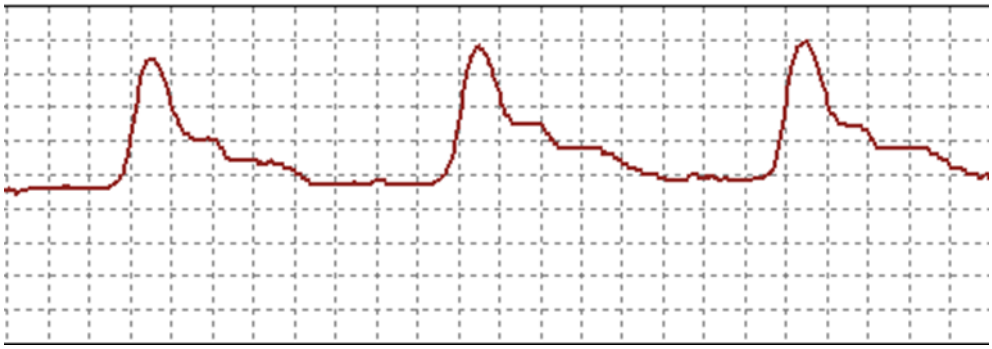
SBPbr: 115 mmHg	**DBPbr**: 55 mmHg	**HR**: 78/min	**MAP**: 75 mmHg
SBPao: 101 mmHg	**AIXbr**: -46.97	**AIXao**: 13.86	**PWVao**: 6.67 m/s

Figure 10. Original pulse pressure waveform of a negative control
Legend: SBPbr - brachial systolic blood pressure, DBPbr - brachial diastolic blood pressure, HR - heart rate, MAP - mean arterial pressure, PP - pulse pressure, SBPao - central systolic blood pressure, AIXao - central augmentation index, AIXbr - brachial augmentation index, PWV - pulse wave velocity



SBPbr: 103 mmHg	**DBPbr**: 44 mmHg	**HR**: 45/min	**MAP**: 64 mmHg
SBPao: 88 mmHg	**AIXbr**: -55.1	**AIXao**: 9.79	**PWVao**: 5.56 m/s

Figure 11. Original pulse pressure waveform of a smoker on the non-smoking day: There are no remarkable differences compared to the waveform of the control person.
Legend: SBPbr - brachial systolic blood pressure, DBPbr - brachial diastolic blood pressure, HR - heart rate, MAP - mean arterial pressure, PP - pulse pressure, SBPao - central systolic blood pressure, AIXao - central augmentation index, AIXbr - brachial augmentation index, PWV - pulse wave velocity



SBPbr: 130 mmHg	**DBPbr**: 76 mmHg	**HR**: 58/min	**MAP**: 94 mmHg
SBPao: 119 mmHg	**AIXbr**: -40.6	**AIXao**: 17.8	**PWVao**: 7.6 m/s

Figure 12. Original pulse pressure waveform of a smoker on the smoking day: The waveform is remarkably distorted due to the shortening of return time (and consequently, the increase of pulse wave velocity), however, no considerable change can be observed in augmentation index values

Legend: SBPbr - brachial systolic blood pressure, DBPbr - brachial diastolic blood pressure, HR - heart rate, MAP - mean arterial pressure, PP - pulse pressure, SBPao - central systolic blood pressure, AIXao - central augmentation index, AIX_{br} - brachial augmentation index, PWV - pulse wave velocity

Table 1 summarizes the brachial systolic blood pressure (SBP_{br}), brachial diastolic blood pressure (DBP_{br}), heart rate, mean arterial pressure (MAP), pulse pressure, SBP_{ao}, Central AIx (AIx_{ao}) and Brachial AIx (AIx_{br}) and PWV values – represented as mean ± standard deviation – in the non-smoking group and in the smoking group on both non-smoking and smoking days.

Legend to Table 1
*Significant difference between smokers on the smoking day and the non-smoking day
#Significant difference between smokers on the smoking day and non-smokers
□Significant difference between smokers on the non-smoking day and non-smokers

SBP_{br} - brachial systolic blood pressure, DBP_{br} - brachial diastolic blood pressure, HR - heart rate, MAP - mean arterial pressure, PP - pulse pressure,
SBPao - central systolic blood pressure, AIXao - central augmentation index,
AIXbr - brachial augmentation index, PWV - pulse wave velocity

		Smokers		Non-smokers
		Non-smoking day	Smoking day	
SBP_{br} (mmHg)	Daytime	127.23±8.41 *	134.11±11.02 *#	120.80±5.77 #
	Night-time	118.64±7.79 □	116.30±9.63 #	106.16±9.10 #□
	All-day	125.15±7.51 □	129.61±9.87 #	117.83±6.23 #□
DBP_{br} (mmHg)	Daytime	71.25±10.47 *	77.11±10.64 *#	68.37±4.87 #
	Night-time	64.40±9.89	62.79±8.84	57.59±5.96
	All-day	69.49±9.57 *	73.43±9.75 *	66.31±4.39
HR (1/min)	Daytime	64.89±9.03 *□	76.09±10.53 *	74.30±8.22 □
	Night-time	55.86±7.50	59.24±8.54	62.08±9.61
	All-day	62.89±8.22 *□	71.63±9.63 *	72.21±8.50 □
MAP (mmHg)	Daytime	89.91±9.30 *	96.11±10.42 *#	85.85±4.53 #
	Night-time	82.48±8.75 □	80.63±8.69	73.78±6.68 □
	All-day	86.04±8.42 *	92.15±9.44 *#	83.48±4.39 #
PP (mmHg)	Daytime	55.98±6.78	57.00±5.80	52.43±5.36
	Night-time	54.24±6.30 □	53.50±5.81	48.57±5.47 □
	All-day	55.66±6.39	56.18±5.53	51.52±5.27
SBPao (mmHg)	Daytime	112.82±10.31	117.59±14.95	111.52±7.39
	Night-time	112.06±11.31	105.04±14.12	100.88±11.70
	All-day	112.33±9.92	114.09±14.53	109.20±8.31
AIX_{ao}	Daytime	15.26±8.45	12.15±9.43	17.79±7.55
	Night-time	23.12±10.49	16.22±8.36	22.78±9.39
	All-day	17.05±8.47	13.41±8.99	18.63±7.87
AIX_{br}	Daytime	-44,20±16,69	-50.34±18.62	-39.20±14.02
	Night-time	-28.68±20.72	-42.30±16.51	-29.35±18.55
	All-day	-40.67±16.73	-47.85±17.76	-37.54±15.54
PWV (m/s)	Daytime	7.00±1.28 *	7.48±1.17 *	7.36±1.11
	Night-time	6.61±1.19	6.73±0.90	6.84±0.84
	All-day	6.86±1.24 *	7.20±1.01 *	7.26±1.08

Table 1. Summary of brachial systolic blood pressure, brachial diastolic blood pressure, heart rate, mean arterial pressure, pulse pressure, central systolic blood pressure, central and brachial augmentation index and pulse wave velocity values – represented as mean ± standard deviation – in the non- smoking group and in the smoking group on both non-smoking and smoking days.

Systolic blood pressure

The systolic blood pressure during daytime was significantly higher among smokers on the smoking day than either among smokers on the non-smoking day (6.88 ± 5.33 mmHg, p=0.02) or non-smokers (13.31 ± 8.46 mmHg, p=0.005). No statistical difference was identified between smokers on the non-smoking day and non-smokers (6.43 ± 6.84 mmHg, p=0.06). Figure 13 represents the daytime brachial systolic blood pressure values in the different groups.

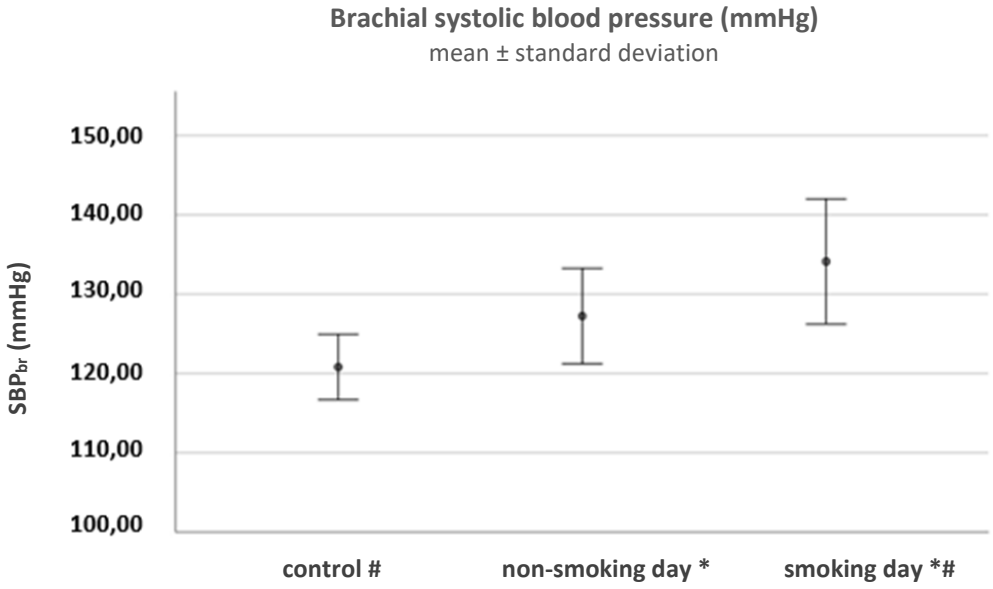


Figure 13. Brachial systolic blood pressure represented as mean ± standard deviation among non-smokers, smokers on the non-smoking day and smokers on the smoking day

* Significant difference between smokers on the smoking day and on the non-smoking day (p=0.02)

Significant difference between smokers on the smoking day and non-smokers (p=0.005)

Legend: SBP_{br}: brachial systolic blood pressure

The systolic blood pressure during night-time was significantly higher among smokers on both non-smoking (12.48 ± 7.96 mmHg, p=0.004) and smoking days (10.14 ± 8.80, p=0.03) than among non-smokers; however, no statistical difference was detected between smokers on the smoking and non-smoking days (p=0.38).

The daily systolic blood pressure was significantly higher among smokers on both non-smoking (7.32 ± 6.48 mmHg, p=0.03) and smoking days (11.78 ± 7.85 mmHg, p=0.006) than among non-smokers; the difference between smokers on the non-smoking and smoking day was not significant (4.46 ± 4.51 mmHg, p=0.05).

Diastolic blood pressure

The diastolic blood pressure during daytime was significantly higher among smokers on the smoking day than among both smokers on the non-smoking day (5.87 ± 4.51 mmHg, p=0.02) and non-smokers (8.74 ± 8.02 mmHg, p=0.04); no statistical difference was identified between smokers on the non-smoking day and non-smokers (p=0.44).

No statistical difference was revealed in diastolic blood pressure during night-time.

The daily diastolic blood pressure was significantly higher among smokers on the smoking day than on the non-smoking day (3.94 ± 3.39 mmHg, p=0.03); however, no statistical difference was found between smokers on the non-smoking day and non-smokers (7.12 ± 7.32 mmHg, p=0.36) or smokers on the smoking day and non-smokers (p=0.06).

Heart rate

The heart rate during daytime was significantly lower among smokers on the non-smoking day than among both non-smokers (9.41 ± 8.11 bpm, p=0.03) and smokers on the smoking day (11.12 ± 5.26 bpm, p=0.001); however, no statistical difference was noticed between smokers on the smoking day and non-smokers (p=0.68).

No statistical difference was identified between the different groups in the case of heart rate during night-time.

The daily heart rate among smokers during the non-smoking day was significantly lower than on both smoking days (8.74 ± 4.26 bpm, p=0.001) and among non-smokers (9.32 ± 7.85 bpm, p=0.02). No difference was found between smokers on the smoking day and non-smokers (p=0.89).

Mean arterial pressure

The mean arterial pressure was significantly higher during daytime among smokers on the smoking day than among both smokers on the non-smoking day (6.20 ± 4.68 mmHg, p=0.02) and non-smokers (10.26 ± 7.81 mmHg, p=0.01); however, no statistical difference was detected between smokers on the non-smoking day and non-smokers (p=0.24).

The mean arterial pressure was significantly higher during night-time among smokers on the non-smoking day than among non-smokers (8.70 ± 7.32 mmHg, p=0.02). Further differences were not proven to be statistically significant.

The daily mean arterial pressure was significantly higher among smokers on the smoking day than among both smokers on the non-smoking day (4.11 ± 3.68 mmHg, p=0.03) and non-smokers (8.67 ± 7.13 mmHg, p=0.02); however, no statistical difference was detected between smokers on the non-smoking day and non-smokers (p=0.15).

Pulse pressure

No statistical difference was revealed between daytime and daily pulse pressure values of different groups.

The pulse pressure during night-time was significantly lower among non-smokers than among smokers on the non-smoking day (5.67 ± 5.54 mmHg, p=0.046); however, further differences were not proven to be statistically significant.

Aortic systolic blood pressure

No statistically significant differences were revealed between the groups during any time of the day.

Aortic and brachial augmentation index

No statistically significant differences were detected between the groups in any time of the day.

Pulse wave velocity

Pulse wave velocity was significantly higher during daytime among smokers on the smoking day than on the non-smoking day (0.48± 0.41, p=0.03). Figure 14 represents the daytime pulse wave velocity values in the different groups. Similarly, the daily pulse wave velocity was significantly higher among smokers on the smoking day than on the non-smoking day (p=0.04). No other statistically significant differences were identified between the other groups in any time of the day.

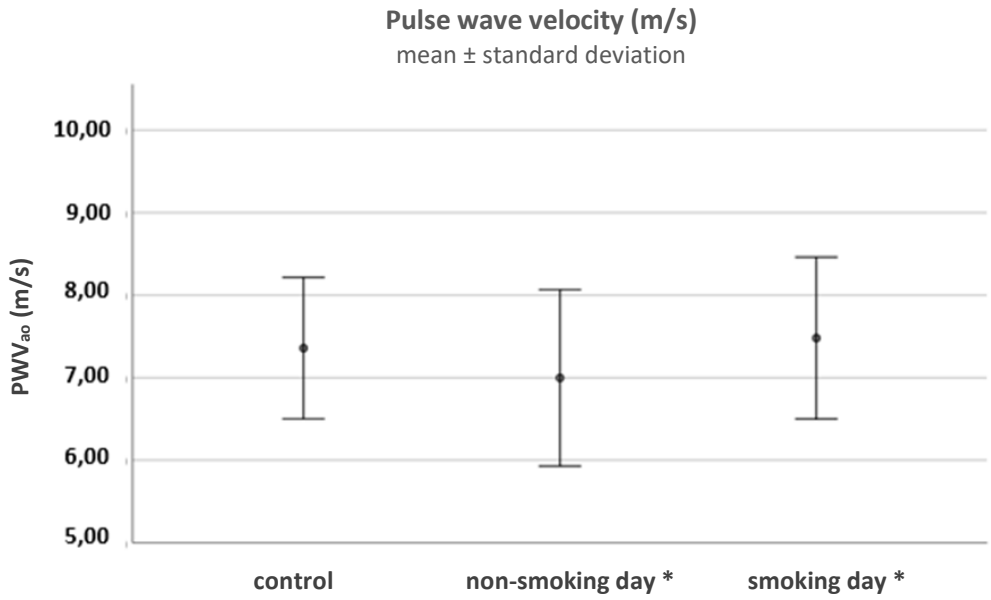


Figure 14. Pulse wave velocity values – represented as mean ± standard deviation – among non-smokers, among smokers on the non-smoking day and among smokers on the smoking day

* Significant difference between smokers on the smoking day and on the non-smoking day (p=0.03)

Legend: PWVao: central pulse wave velocity

Discussion

To the best of our knowledge, no data on 24-hour or self-controlled stiffness parameters in smokers has been published to date. Our results confirm former observations in general, nevertheless add important novel aspects to those at several points.

The effect of smoking on peripheral blood pressure values remained a disputed issue, blood pressure values are expected to be higher in smokers due to sympathetic stimulation, which is confirmed by numerous studies [58]. However, others – using a single measurement method – did not find difference [52, 59], whereas inverse relationship (i.e. lower systolic and diastolic blood pressure results in smokers) was also published [60]. In our research, the highest systolic blood pressure values were measured during daytime in smokers on the smoking day (134.11 ± 11.02 mmHg). This value improved (with 6.88 ± 5.33 mmHg) in smokers on the non-smoking day to a similar systolic blood pressure value of non-smokers. The same claim is proven to be true for daily systolic blood pressure results. The analysis of night-time systolic blood pressure results revealed that smokers had higher values on both smoking and non-smoking days than non-smokers; however, no significant improvement could be observed among smokers between the non-smoking and smoking days supporting the potent subchronic effect of smoking on diastolic blood pressure.

Diastolic blood pressure values during daytime were significantly higher in smokers on the smoking day than on the non-smoking day or in non-smokers. No difference was found between the results of smokers on the non-smoking day and non-smokers, though, suggesting that the subchronic effect of smoking on diastolic blood pressure is less substantial than on systolic blood pressure. The latter is partially confirmed by the fact that no significant differences were found between the different groups during night-time.

Tobacco smoking is considered to cause an acutely and chronically accelerated heart rate due to sympathetic stimulation confirmed by numerous research data [59, 60, 61]. A study in 2013 found that smokers had higher resting heart rate, however they showed lower heart rate increase during exercise [62]. Thus, the heart rate analysis in our study provided partially surprising findings. Evaluation of the results of smokers alone revealed that these were consistent with previous data, i.e. the heart rate of smokers on the smoking day was 11.20 ± 5.18 bpm higher than on the non-smoking day. Interestingly, the comparison with

the results of non-smokers revealed that there was no difference between the values of non-smokers and smokers on the smoking day, but the value of smokers on the non-smoking day was proven to be 9.41 ± 8.10 bpm lower than that of non-smokers. A similarly designed study published in 2014 examining adolescents before and after smoking cessation and negative controls found that resting heart rate results were in accordance with expectations, the heart rate of smoking subjects was significantly lower than the heart rate of healthy controls, though [63]. The authors explained this result with the different activity of participants, what is – based on the same orders given to participants – highly unlikely in our study. As all participants were involved in normal daily activities these results could rather be considered a consequence of improper heart rate adaptation during exercise similarly to subjects in the study of Papathanasiou et al. [62]. The decrease of systemic vascular resistance – confirmed by the decreasing blood pressure values – resulting in an increased cardiac output associated with the secondary decrease of heart rate could further explain this phenomenon, however, further examinations should be planned and performed to evaluate this observation.

Mean arterial pressure values during daytime and all-day were significantly higher among smokers on the smoking day than both smokers on the non-smoking day and non-smokers, and similarly to systolic and diastolic blood pressure no difference was found between smokers on the non-smoking day and non-smokers. The values during night-time appeared to be lower in non-smokers than in smokers on the non-smoking day, which is likely to reflect the effect of non-significant night-time difference in diastolic blood pressure between these groups.

Although significant differences were observed in both daytime and daily systolic and diastolic blood pressures, the analysis of peripheral pulse pressure revealed no statistically significant differences in daytime or daily pulse pressure values suggesting that systolic and diastolic blood pressure values incremented proportionally as a result of smoking. During night-time the pulse pressure among non-smokers was lower than among smokers on the non-smoking day reflecting the greater increment in systolic than diastolic blood pressure (differences in systolic and diastolic blood pressure were 12.48 ± 7.96 mmHg and 10.14± 8.80 mmHg, respectively).

As more invasive and non-invasive studies demonstrated, increased augmentation index is associated with an increased risk for coronary artery disease [15, 64]. Augmentation index was proven to be significantly lower after a 1-year-long cessation period [59] and appeared to be higher in chronic smokers compared to non-smokers with single measurement [52]. In our study, no statistically significant differences were found between the tested groups. Therefore, one day of abstinence seems to have no effect on brachial and aortic augmentation index.

According to the Strong Heart Study pulse wave velocity as a direct representative of vascular stiffness has been related to cardiovascular risk in several patient populations [65]. Pulse wave velocity was found to be decreased after a 1-year-long smoking cessation [59] and immediately after cigarette smoking as well [52]. The assessment of our pulse wave velocity results revealed that – as expected, based on the sympathetic stimulation caused by tobacco smoking – pulse wave velocity during daytime and all-day was higher among smokers on the smoking day than on the non-smoking day. Pulse wave velocity is considered to reflect the actual state of vessels. Our results confirm this claim, as pulse wave velocity values were higher among smokers on the smoking day than on the non-smoking day. Nevertheless, the fact that pulse wave velocity values improved to those of non-smokers during the one-day long non-smoking period suggests that the analysed vascular changes are reversible in this young population.

Limitations

The main limitations of the study included the difficulty in recruiting this type of volunteer – i.e. the majority of potential “light smoker” participants declined participation due to the prolonged 24-hour non-smoking period – resulting in consequent problems during statistical analysis and the evaluation of results. Further examinations are required to reveal further differences in a greater population. The relative great number of invalid measurements resulting from the sensitivity of the equipment to move has led to further difficulties during analysis and evaluation.

Conclusion

Although the relationship of smoking and cardiovascular risk factors has long been investigated, contradictory data was published (e.g. the effect of smoking on blood pressure) and open points have remained. Only a few self-controlled studies exist in the field, mainly with limited measurement spectrum and/or focusing on the differences after a longer period (one week, one year). Our study demonstrates a database capable of comparing various parameters between smokers during smoking day, smokers during non-smoking day and non-smokers. The changes in systolic and diastolic blood pressure, pulse pressure and mean arterial pressure values followed the expectations. The unexpected changes in heart rate are likely to demonstrate an improper heart rate adaptation to everyday activities or a secondary decrease in heart rate due to the decreasing systemic vascular resistance and increasing cardiac output. Nevertheless, no difference was found in brachial and central augmentation index and central systolic blood pressure values, whereas pulse wave velocity values significantly improved during the one-day long non-smoking period suggesting that pulse wave velocity is the most sensitive parameter to smoking among the tested parameters.

THE EFFECT OF SMOKING ON THE CIRCADIAN RHYTHM OF CARDIOVASCULAR PARAMETERS

Introduction

Blood pressure is proven to follow a daily circadian rhythm with a physiological decrease during the night and a rise during the transition from sleep to wakefulness with intraarterial and non-invasive ambulatory 24-hour blood pressure (ABPM) measurements [66-68]. This morning blood pressure surge appears to be 20-25 mmHg in systolic and 10-15 mmHg in diastolic blood pressure. [68] However, due to further studies both systolic and diastolic blood pressure values are the highest late in the afternoon. [68-70] External factors influencing the blood pressure variation include light-cycle, external temperature, posture, physical or mental activities and food consumption [68, 71]; whereas centrally determined blood pressure oscillations [72], circadian fluctuation of autonomic nervous and endocrine systems such as cortisol, insulin, melatonin, renin and aldosterone, the antioscillatory effect of the baroreflex [73] and the intrinsic circadian activity of the brain, heart, kidney and vascular cells [71, 74-75] can be found among internal factors. The utilization of 24-h ambulatory blood pressure monitoring has revealed that besides mean daytime blood pressure, certain characteristics of daily blood pressure variation including an exaggerated early morning surge [76] and the lack of nocturnal dip [77-80] are associated with the increased risk of cardiovascular diseases and end-organ damage. The number of cardiovascular events as myocardial infarction [81-83], ischemia, sudden cardiac death [84-85] and stroke [86-87] also vary throughout the day with a morning peak. Nevertheless, a study revealed that this correlation disappeared in the case of myocardial ischemia if the patients had been treated with ß-blocker prior to the event [82].

Beyond traditional risk factors arterial stiffness is also proven to predict cardiovascular complications [18, 88]. The gold standard of arterial stiffness assessment is currently considered to be the aortic pulse wave velocity [89]. The Framingham Heart Study examined pulse wave velocity, augmentation index, carotid-brachial pressure amplification and central pulse pressure in 2232 participants in a multivariable model demonstrating that

higher aortic PWV was associated with a 48% increase in cardiovascular disease risk. Moreover, integrated discrimination improvement was 0.7% after adding PWV to a standard risk model [90]. A few further studies analysed the diurnal variation of pulse wave velocity, augmentation index and central blood pressure limited to the evaluation of differences between awake and asleep periods. A Uruguayan study demonstrated significant night-time decrease of pulse wave velocity and pressure amplification (peripheral pressure/central pressure) parallel with a less outstanding decrease of central pressure and a significant increase of systolic augmentation [91]. A study examining circadian variation of wave reflections in healthy individuals demonstrated significant daytime changes in heart rate corrected augmentation index and heart rate with one peak in the morning and another in the late afternoon [92]. Another study analysing carotid-to-radial pulse wave velocity in young and healthy men at three different time points (8:00, 12:00, 17:00) found significantly higher pulse wave velocity at 8:00 than at any other time points [93]. Nevertheless, Drager and colleagues observed no significant differences when analysing systolic, mean and diastolic blood pressure and pulse wave velocity at four different time points (8:00, 12:00, 16:00, 20:00) [94].

Many studies discuss the topic of various cardiovascular parameters and smoking, however only one addressed its effect on the well-known circadian rhythm of the aforementioned parameters. Adan et colleagues compared the heart rate and the systolic and diastolic blood pressure of smokers and non-smokers hourly between 8:00 and 21:00 and revealed that smokers reached the daily peak value of heart rate an hour later than non-smokers. Although the test and control groups did not show significant difference between the mean heart rate, systolic or diastolic blood pressure levels, hourly analysis assessed several time intervals, where significant difference could be identified between the test and control groups [95].

Aims

First of all, our study aimed to determine the natural circadian changes of arterial stiffness parameters. Afterwards, the alteration in the circadian pattern of hemodynamic and arterial stiffness parameters were expected to be determined in smokers.

Methods

Ten healthy smoker volunteers participated in the first phase of our study between 1st April 2015 and 31st December 2015, who were examined for 24 hours with a non-invasive ambulatory oscillometric device (Arteriograph 24 distributed by Tensiomed Kft Budapest). Day and night periods were adjusted individually; brachial systolic and diastolic blood pressure, heart rate and arterial pulse pressure waveform were measured, aortic systolic blood pressure, aortic augmentation index, brachial augmentation index and aortic pulse wave velocity were derived, whereas pulse pressure and mean arterial pressure were calculated in every 20 minutes during waking and every 40 minutes during sleeping hours. Augmentation index was calculated as a difference of the reflected (second, P2) and ejected (first, P1) peaks of the central pressure waveform expressed as a percentage of pulse pressure.

In the second phase of the study, ten healthy, age- and BMI-matched non-smoker volunteers were examined for 24 hours with the same method between 1st July 2017 and 31st December 2017.

The consumption of alcohol-containing beverages or drugs were prohibited during the participation period as well as physical exertion outside usual daily activities. Volunteers with any chronic disease may affecting cardiovascular function (e.g. chronic kidney disease, congenital heart defect or hypertension) and those regularly consume alcohol or drugs were excluded from the study.

Invalid data (due to measurement error based on excessive movement during measurement) were eliminated during individual data control resulting in an average of 46 remaining values per day per parameter. Missing and invalid data were omitted from further statistical analysis. During circadian pattern analysis waking hours were divided into 4-hour-long periods (awakening – awakening + 3 hour and 59 minutes (first period); awakening + 4 hours – 7 hours 59 minutes (second period); awakening + 8 hours – 11 hours and 59 minutes (third period) and awakening + 12 hours – asleep (fourth period) starting with awakening and finishing with sleep onset (thus, the length of the last period may vary). IBM SPSS Statistics v25.0 was utilized to perform socio-demographic and statistical analysis. The samples were tested for normality using the one-sample Kolmogorov-Smirnov test.

The results obtained during different periods of the day in the two groups (non-smokers, smokers), expressed as means ± standard errors were compared to the daytime average of the dedicated parameter with paired samples T-test. Significance level (rounded to two digits) ≤ 0.05 was considered significant.

Results

Brachial systolic blood pressure

As represented in Figure 15, brachial systolic blood pressure in non-smokers was significantly higher during period 3 (125.15 ± 1.72 mmHg) than the daily average (120.80 ± 1.82 mmHg; p=0.003). In smokers, no significant differences could be identified in brachial systolic blood pressure between the daily average and any of the time periods.

Significant difference was observed between the daytime mean brachial systolic blood pressure value of non-smokers (120.80 ± 1.82 mmHg) and smokers (134.11 ± 3.49 mmHg; p=0.003), as well between the mean brachial systolic blood pressure value of non-smokers and smokers during period 1 (118.44 ± 2.63 mmHg, 134.27 ± 3.87 mmHg, p=0.03), period 2 (120.55 ± 2.68 mmHg, 137.16 ± 4.49 mmHg, p=0.005) and period 4 (118.96 ± 2.35 mmHg, 131,29 ± 3.77 mmHg, p=0.013).

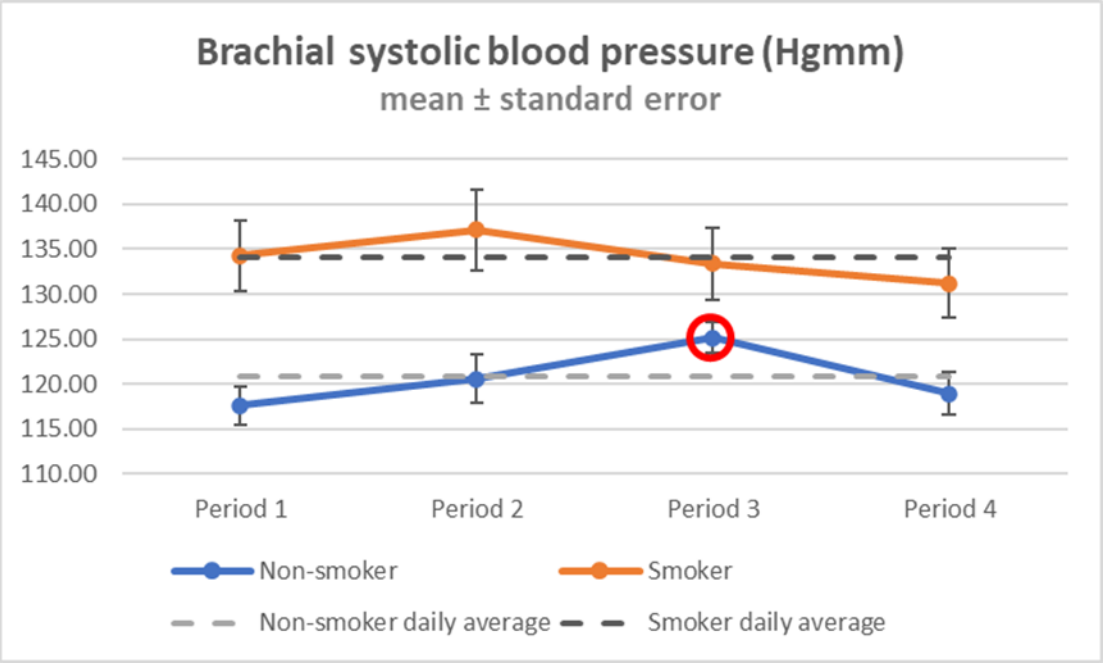


Figure 15. Brachial systolic blood pressure values among non-smokers and smokers during different time periods

Brachial diastolic blood pressure

As Figure 16 shows, diastolic blood pressure during period 3 (71.32 ± 1.92 mmHg) was significantly higher in non-smokers than the daily average (68.37 ± 1.54 mmHg; p=0.035). In smokers, no significant difference could be shown between any time period and the daily average.

Significant difference was identified between the daytime mean brachial diastolic blood pressure value of non-smokers (68.37 ± 1.54 mmHg) and smokers (77.11 ± 3.36 mmHg, p=0.03) as well as between the mean brachial diastolic blood pressure value of non-smokers and smokers during period 1 (66.84 ± 1.58 mmHg, 79.20 ± 4.00 mmHg, p=0.01) and period 2 (68.34 ± 2.05 mmHg, 78.51 ± 4.02 mmHg, p=0.037).

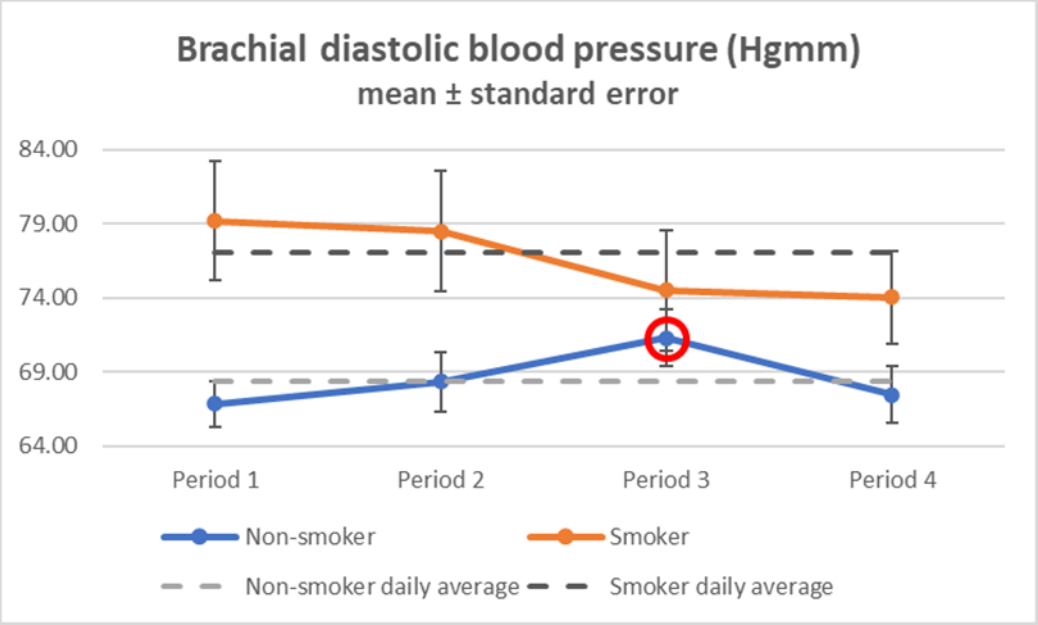


Figure 16. Brachial diastolic blood pressure values among non-smokers and smokers during different time periods

Mean arterial pressure

Figure 17 highlights a significant difference of mean arterial blood pressure during period 3 (89.26 ± 1.50 mmHg) in non-smokers compared to the daily average (85.85 ± 1.43 mmHg; p=0.008), whereas no statistical difference appeared to be between time periods and the daily average in smokers.

Significant difference was revealed between the daytime average of mean arterial pressure value of non-smokers (85.85 ± 1.43 mmHg) and smokers (96.11 ± 3.29 mmHg, p=0.01) as well as the average of mean arterial pressure of non-smokers and smokers during period 1 (84.04 ± 1.71 mmHg, 97.55 ± 3.88 mmHg, p=0.005), period 2 (85.74 ± 2.13 mmHg, 98.05 ± 3.99 mmHg, p= 0.014) and period 4 (84.64 ± 1.87 mmHg, 93.12 ± 3.09 mmHg, p=0.031).

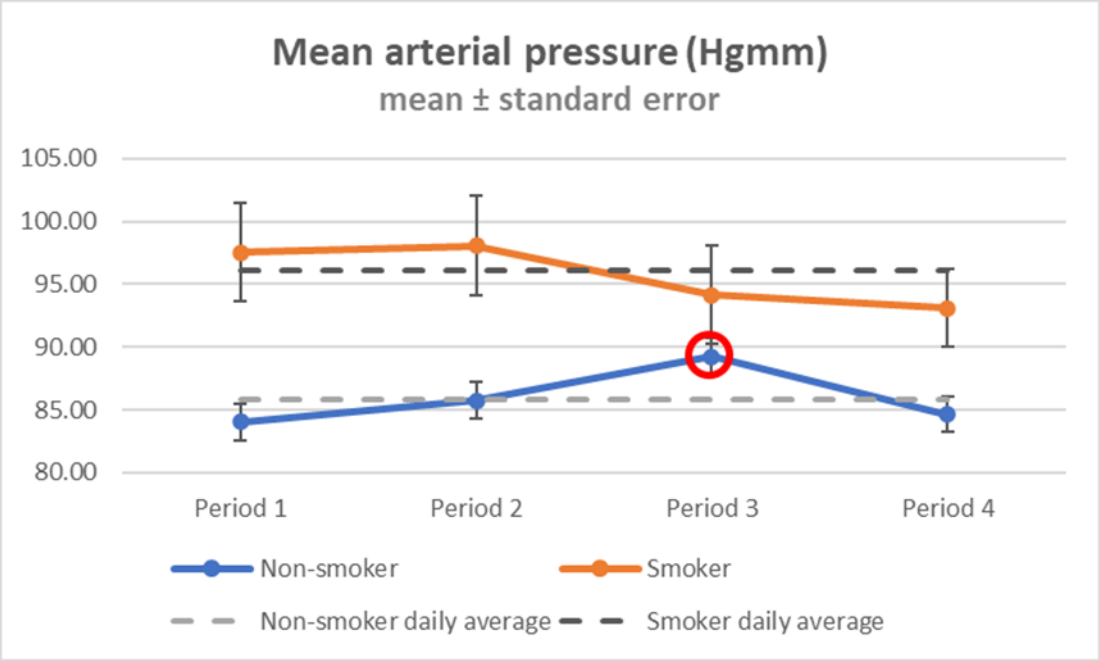


Figure 17. Mean arterial pressure values among non-smokers and smokers during different time periods

Heart rate

As demonstrated in Figure 18, the heart rate in non-smokers during period 2 (77.17 ± 3.33 bpm) and period 3 (76.70 ± 3.03 bpm) was significantly higher than the daily average (73.80 ± 2.31 bpm; p=0.045 and p=0.032, respectively).

There were no statistical differences between the mean heart rate value of non-smokers and smokers during the daytime or any periods.

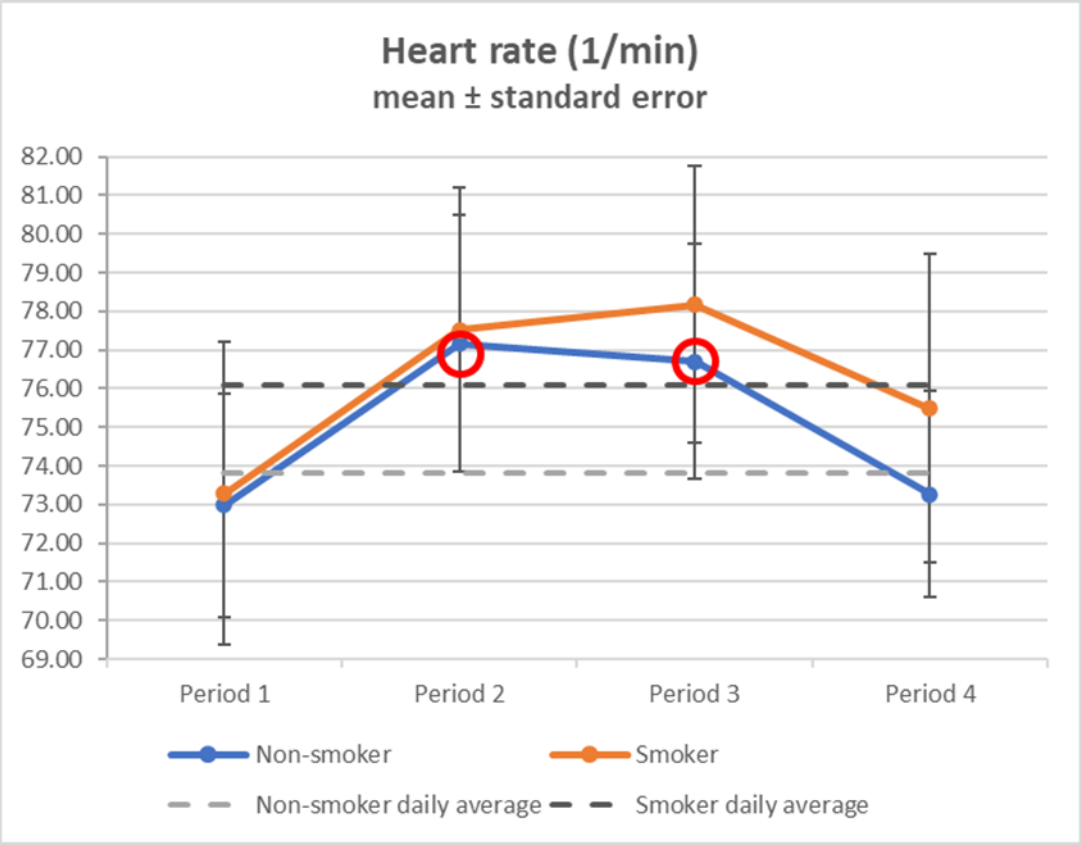


Figure 18. Heart rate values among non-smokers and smokers during different time periods

As represented in Figure 19, pulse wave velocity in non-smokers during period 2 (7.81 ± 0.40 m/s) and period 3 (7.70 ± 0.45 m/s) was significantly higher than the daily average (7.36 ± 0.37 m/s; p=0.018, p=0.022, respectively).

No statistical differences were found between the mean pulse wave velocity value of non-smokers and smokers during the daytime or any periods.

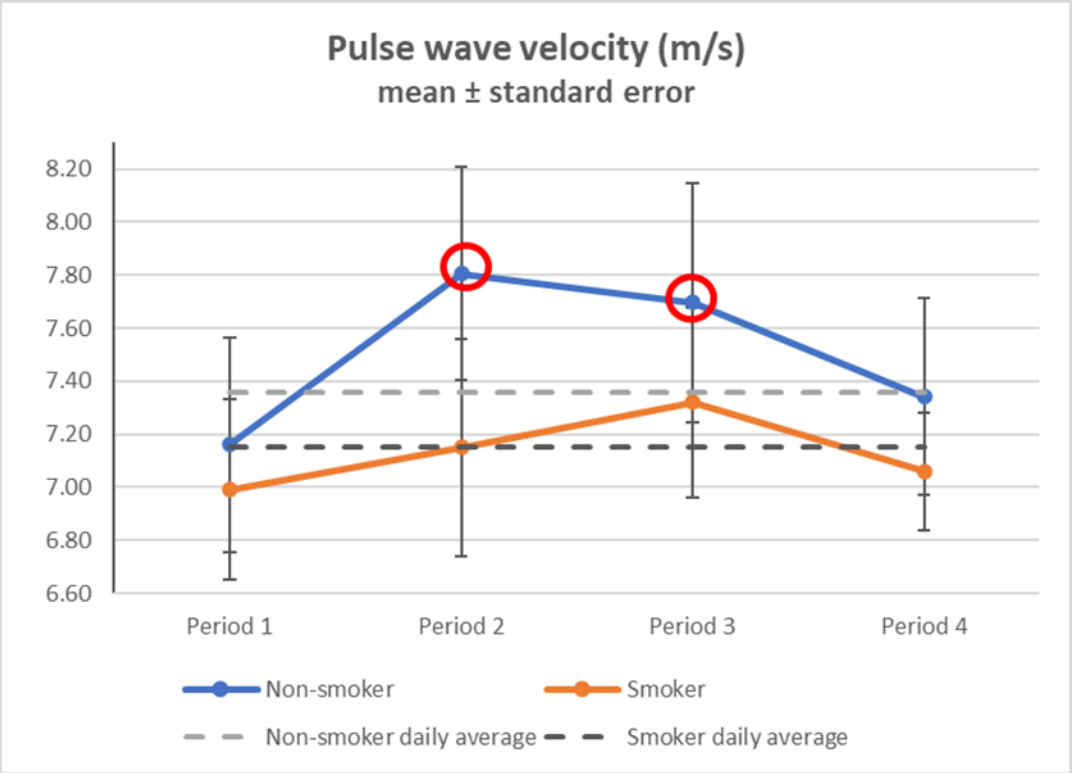


Figure 19. Pulse wave velocity values among non-smokers and smokers during different time periods

Augmentation indices

As Figure 20 and 21 show, brachial (-56.15 ± 5.81) and central augmentation indices (9.21 ± 2.94) in smokers were significantly lower during period 3 than the daily average (-50.34 ± 6.58, p=0.002; 12.16 ± 3.33, p=0.002, respectively).

No statistical differences were recognized between the mean augmentation index values of non-smokers and smokers during the daytime or any periods.

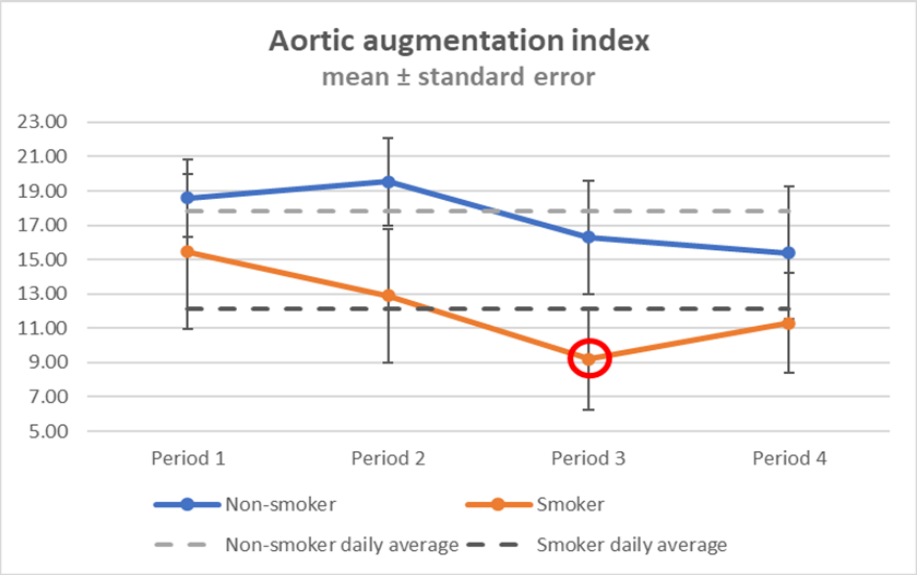


Figure 20. Aortic augmentation index values among non-smokers and smokers during different time periods

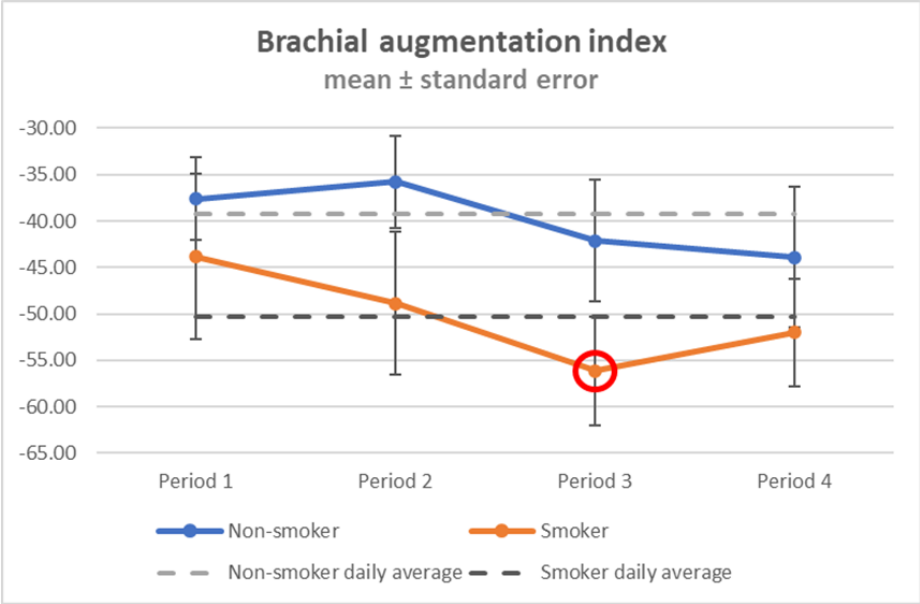


Figure 21. Brachial augmentation index values among non-smokers and smokers during different time periods

Central systolic blood pressure

As represented in Figure 22, central systolic blood pressure was significantly higher in non-smokers during period 3 (114.05 ± 2.53 mmHg) than the daily average (111.52 ± 2.46 mmHg, p=0.033).

No statistical differences were revealed between the mean central systolic blood pressure value of non-smokers and smokers during the daytime or any periods.

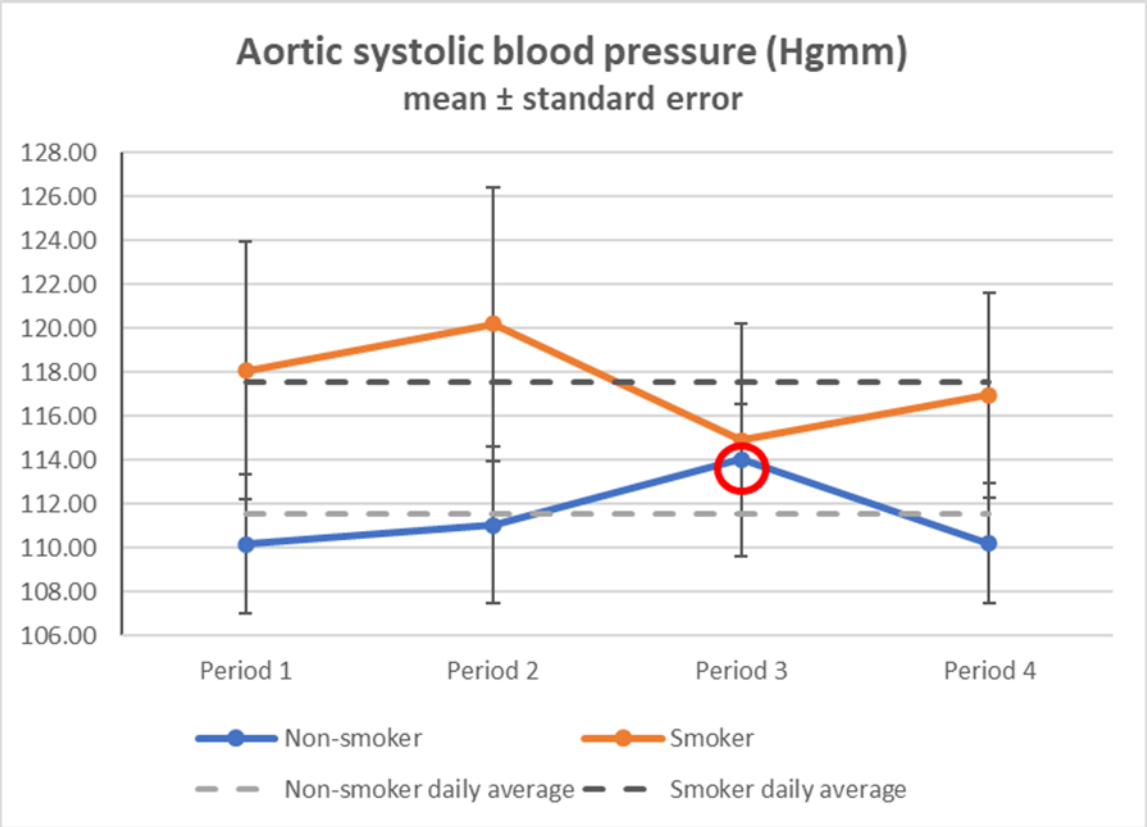


Figure 22. Aortic systolic blood pressure values among non-smokers and smokers during different time periods

As demonstrated in Figure 23, neither in non-smokers nor in smokers were any differences in pulse pressure identified between any time periods and the daily average.

No statistical differences were observed between the mean pulse pressure value of non-smokers and smokers during the daytime or any periods.

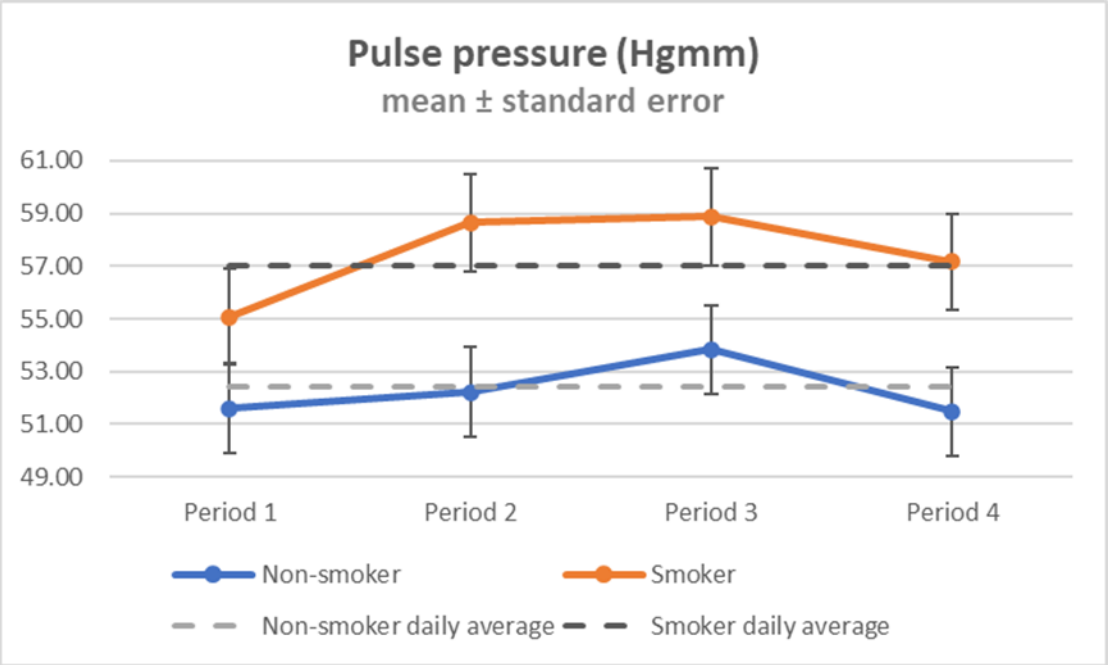


Figure 23. Pulse pressure values among non-smokers and smokers during different time periods

Discussion

As most physiological factors, cardiovascular parameters including blood pressure and heart rate values are proven to follow a circadian rhythm [66-70] and the frequency of cardiovascular events follow this rhythm [81-87]. More studies have demonstrated that any deviation from the normal circadian rhythm – both an exaggerated morning surge [76] and both diminished or lacking night-fall [77-79] – can lead to an increased frequency of end-organ damage. With the observation of shift workers, it was also demonstrated that blood pressure rather depends on activity than the time of the day [70].

When analysing brachial systolic and diastolic blood pressure and mean arterial pressure, beside the significant difference of daytime mean values between non-smokers and smokers, our study reveals an obvious and significant daily peak among non-smokers (period 3, awakening + 8 hours – 11 hours and 59 minutes) coinciding with the increased afternoon activity after work. This peak disappears in the case of systolic and diastolic blood pressure and mean arterial pressure among smokers resulting in a more even curve with a higher mean value, though. The analysis of heart rate curves revealed a double peak among non-smokers, the heart rate values of period 2 and period 3 were significantly higher than the daytime mean. Due to a diminished decrease of heart rate during period 3 and period 4 a more even curve formed among smokers leading to the lack of daily peak.

Studies on arterial stiffness supports that stiffness parameters play an important role in cardiovascular risk estimation [18, 88, 90]. The very limited literature on the circadian rhythm of stiffness parameters suggests a similar variation of stiffness parameters to that of other cardiovascular factors including a night-time decrease in pulse wave velocity, pressure amplification and central pressure parallel with a night-time increase of systolic augmentation [91]; morning and late afternoon peak in heart rate corrected augmentation index and heart rate [92] and an increased carotid-to-radial pulse wave velocity in the morning compared to any other time points during the day [93]. Controversially, another study found no differences in systolic or diastolic blood pressure or pulse wave velocity at four different time points [94]. The central systolic blood pressure curve of both non-smokers and smokers resembles that of systolic and diastolic blood pressure with the same peak (period 3) among non-smokers coinciding the increased late afternoon activity.

Although statistical significance could not be identified between non-smokers and smokers either for daytime mean or for the mean value of any periods in the case of pulse wave velocity, contrary to the more even curve of smokers, non-smokers represent a double peak, similar to that of heart rate: the mean pulse wave velocity of period 2 and period 3 were significantly higher than the daytime mean. Interestingly and contrary to the parameters mentioned above, the augmentation index curve of smokers shows a negative peak at period 3, whereas the augmentation index values of non-smokers form a more even curve. The study of Boggia et al. may assist in the resolution of this discrepancy revealing the opposite changes of systolic augmentation compared to pulse wave velocity, pressure amplification and central pressure [91]. Considering this opposite change a more even curve would form among non-smokers, whereas a peak would generate among smokers.

Conclusions

Regarding the circadian rhythm of cardiovascular parameters among non-smokers, the results of our study are partly in accordance with previous studies and anticipations with a significant peak observed at almost all substantial parameters. The only exceptions appeared to be augmentation index values, where a more even curve formed indicating an opposite change of augmentation index values compared to other parameters. Nevertheless, among smoking participants a more even curve could be observed indicating a diminished circadian change of these parameters. Further studies are required to reveal the extent of this diminished circadian change and its effect on the daily distribution of cardiovascular diseases, as well as the importance of examination time.

AB0 BLOOD GROUPS AS CARDIOVASCULAR RISK FACTORS

Introduction

Cardiovascular diseases account for 45% of deaths in Europe. The occurrence of cardiovascular diseases increases with age in both developing and developed countries. The number of patients in Europe with coronary heart disease is estimated to 20 million and is expected to increase further [1]. On average, approximately 15 000 people are diagnosed yearly in Hungary with acute myocardial infarction that has a 1-year mortality of 20-25% [2]. As organic manifestations of atherosclerosis, cardiovascular diseases including coronary heart diseases, ischemic cerebrovascular diseases and peripheral vascular diseases account for the major medical challenge of developed countries, as the increasing number of deaths, disability and hospital admissions resulting from them represents a greater economic burden than the economic burden of all other diseases. The mortality structure of cardiovascular diseases has substantially changed during the last decades: in the early 1990s, the majority of cardiovascular deaths occurred due to myocardial infarction and cerebrovascular diseases, nowadays chronic ischemic heart disease resulting in heart failure leads most frequently to death [1]. It is not a coincidence, that studying the risk factors and prevention methods of atherosclerosis triggering the development of most cardiovascular diseases reflects a growing interest.

Hence, the complex examination, therapy of patients and – most of all – prevention becomes particularly important. Well-known risk factors of myocardial infarction, stroke and peripheral vascular disease include hypertension, diabetes mellitus, dyslipidaemia, physical inactivity, unhealthy diet, obesity, smoking, alcohol consumption and the marginal number of screening tests. Besides, recent studies revealed further risk factors. Certain genetic disorders, increased blood viscosity, increased fibrinogen concentration, homocysteine accumulation resulting in blood vessel wall disorders and increased C-reactive protein (CRP) value should all be considered a threat [3]. Furthermore, the results of numerous studies suggest that AB0 blood groups might play a role in cardiovascular risk

stratification, nevertheless, these studies are controversial, more of them has not found a relationship between AB0 blood groups and the development of cardiovascular diseases [96-105].

The altering concept of cardiovascular prevention

The holistic approach has recently led to a significant conceptual change in the field of cardiovascular prevention. The primary goal was earlier to prevent coronary heart disease as the most frequent cause of death and morbidity. Novel intervention studies clarified that preventive measures of coronary heart disease do not only decrease the number of coronary events (myocardial infarction, sudden death, etc.) and coronary revascularization procedures, but significantly reduce the number of ischemic cerebrovascular and peripheral vascular events as well. Similarly, preventive measures against cerebrovascular diseases reduce the number of coronary and peripheral vascular events and the appropriate treatment for peripheral arterial disease reduces the number of coronary and cerebrovascular events. This can be explained with a common underlying disease, namely the atherosclerosis, destroying the whole vascular system that manifests at one time with only one target organ disease. Regarding the aforementioned facts, the necessity of prevention is determined based on the risk of occurring any kind of vascular event (not only coronary events).

Symptomless persons with markedly high level of one risk factor or parallel presence of more cardiovascular risk factors belong to priority level 2 due to the large cardiovascular risk. Both cases require intensive lifestyle modification and the sufficient influence of risk factors in order to significantly decrease the total cardiovascular risk. Weight should be decreased until abdominal circumference becomes < 88 cm in women and < 102 cm in men. Recommended values are < 140/90 mmHg for blood pressure, < 5 mmol/l for cholesterol level and < 3.0 mmol/l for LDL cholesterol level. When more risk factors are present and blood pressure value remains under 160/100 mmHg, acetylsalicylic acid is recommended. Statin should be prescribed for elevated total cholesterol or LDL cholesterol level [3].

Blood group determination

Although cardiovascular diseases represent a serious medical burden worldwide, significant geographic differences can be observed in their occurrence even within Europe. A study suggested that the geographic differences in the distribution of blood groups could explain the geographic differences in the occurrence of cardiovascular diseases [106].

International data

Regarding AB0 blood groups blood group 0 and A are typically frequent, whereas the frequency of blood group B rises from West to East [107]. The almost total absence of blood group B is characteristic for aboriginal Australians and American Indians (Bororo and Navajo tribes) [108]. Blood group 0 is noticeably frequent among Spanish Basques and French people of Basque descent. Blood group 0 occurs with such frequency only among Irish, Scottish and Welsh people of Celtic descent and indigenous Icelanders and Sardinians. Nevertheless, the Basques differ from the listed nations in the remarkable rarity of blood group B and the remarkable frequency of Rh negativity among Western Europeans [107, 109].

Hungarian data

The blood group distribution of the Hungarian population was mapped by Tauszik et al. Table 2 represents the blood group distribution of the Hungarian population by the frequency of AB0 and Rh(D) blood groups between 2000-2008. The data on AB0 distribution in 2014 is based on the verbal statement of the Hungarian National Transfusion Service.

	0	A	B	AB	Rh neg	Rh pos
National mean 2000-2008	**31.3**	**41.6**	**18.1**	**9.0**	**16.6**	**83.4**
National mean 2014	**32**	**42**	**15.5**	**10.5**		

Table 2. Blood group distribution of Hungarian residents based on the aggregated county data and verbally communicated data of the Hungarian National Blood Transfusion Service

Aims

More studies suggested a relationship between AB0 blood groups and cardiovascular risk, however, the results of other studies contradict this theory. The aim of our study was to confirm the hypothesis that blood group 0, B and AB occur less frequently than blood group A among people undergone surgical intervention or heart surgery after an acute cardiovascular event compared to patients without cardiovascular events in their medical history (control group).

Materials and methods:

The study population consisted of 63 men and 112 women diagnosed with acute cardiovascular event at the Department of Emergency Medicine at the University of Pécs and undergone surgical intervention or heart surgery at the Heart Institute at the University of Pécs afterwards. Patients with NSTEMI requiring no surgical intervention or heart surgery were excluded from the study. Data on AB0 blood group distribution was compared to that of the control group consisting of 30 men and 54 women without acute cardiovascular events in their history. Gender, body mass index (BMI) calculated from body height and body mass, smoking, alcohol consumption, the presence of dyslipidaemia, hypertension, diabetes mellitus and peripheral vascular disease were recorded, if such data was available in the medical history. Patients with BMI over 30 were considered overweight.

Statistical analysis

Demographic, comorbidity and medication data were represented as prevalence (the absolute number of cases compared to the total number of the group) and percentage. Age comparison was performed with independent samples T-test and further statistical analyses were performed with chi-square test or Fisher's exact test, if an expected cell count was less than 5. Significance level (rounded to two digits) ≤0.05 was considered significant. Data analysis was performed with SPSS v25.0 software.

Results

In order to prevent age or gender bias on the examined parameter, patient and control groups were matched for age (64.74 ± 8.53 years, 65.24 ± 13.07 years, respectively, p=0.795) and gender (prevalence of men: 36.0%, 35.7%, respectively, p=0.964).

Among the 175 patients 94 (53.7%) had blood group A and 81 (46.3%) had blood group 0, B or AB. From the 84 people in the control group 30 (35.7%) had blood group A and 54 (64.3%) had blood group 0, B or AB. As Figure 24 demonstrates, blood group A occurred significantly more frequently in the patient group than in the control group (p=0.007).

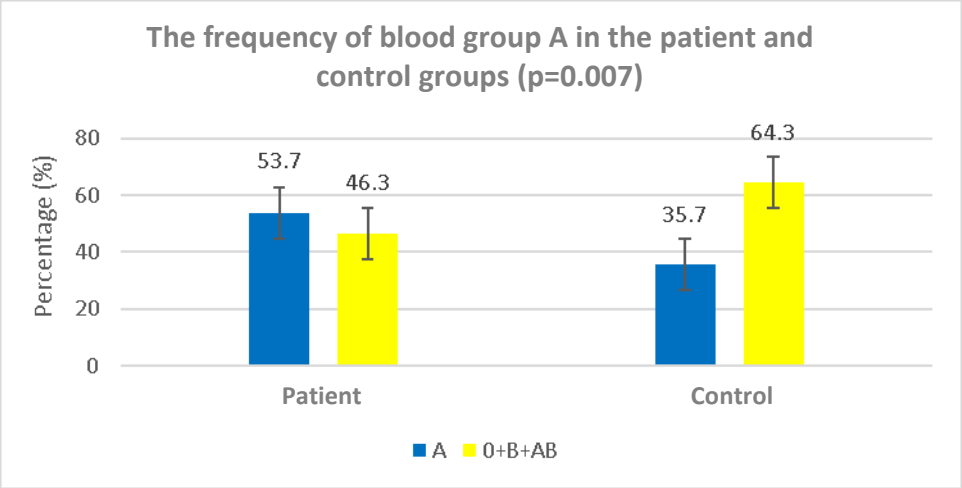


Figure 24. The frequency of blood group A in the patient and control groups

As Table 3 represents, the comparison of patients with blood group A and patients with blood group 0, B or AB compared by gender, smoking, alcohol consumption, obesity, hypertension, diabetes mellitus, dyslipidaemia and vascular diseases revealed that vascular diseases occurred significantly less frequently among patients with blood group 0, B or AB (56.8%) than among patients with blood group A (71.3%, p=0.046).

	Patients with blood group A		Patients with blood group 0, B and AB		p
	Percentage (%)	Case number (positive/total)	Percentage (%)	Case number (positive/total)	
Male gender	64.9	33/94	63.0	30/81	0.791
Smoking	54.3	51/94	59.3	48/81	0.505
Obesity	35.1	33/94	28.4	23/81	0.343
Regular alcohol consumption	11.7	11/94	14.8	12/81	0.543
Hypertension	92.6	87/94	86.4	70/81	0.183
Diabetes	43.6	41/94	33.3	27/81	0.164
Dyslipidaemia	70.2	66/94	64.2	52/81	0.397
Vascular disease	71.3	67/94	56.8	46/81	**0.046**

Table 3. Comparison of patients with blood group A and blood group 0, B and AB

The results of the comparison between control group members with blood group 0, B or AB and control group members with blood group A are summarized by Table 4. No significant differences were revealed by the comparison of these subgroups.

	Controls with blood group A		Controls with blood group 0, B and AB		
	Percentage (%)	Case number (postive/total)	Percentage (%)	Case number (positive/total)	p
Male gender	30.0	9/30	38.9	21/54	0.415
Smoking	23.3	7/30	20.4	11/54	0.751
Obesity	10.0	3/30	25.9	14/54	0.097
Regular alcohol consumption	3.3	1/30	13.0	7/54	0.249
Dyslipidaemia	13.3	4/30	20.4	11/54	0.420
Hypertension	56.7	17/30	75.9	41/54	0.067
Diabetes	16.7	5/30	35.2	19/54	0.072
Vascular disease	13.3	4/30	7.4	4/54	0.448

Table 4. Comparison of control group members with blood group A and blood group 0, B and AB

The comparison results of patients with blood group A and control group members with blood group A are summarized by Table 5. Obesity (10.0%), smoking (23.3%), dyslipidaemia (13.3%), hypertension (56.7%), diabetes (16.7%) and vascular diseases (13.3%) occurred significantly less frequently among control group members with blood group A than among patients with blood group A (35.1%, p=0.008; 54.3%, p=0.003; 70.2%, p<0.001; 92.6%, p<0.001; 43.6%, p=0.008; 71.3%, p<0.001). Parameters with significant differences between the two subgroups are summarized by Figure 25.

	Patients with blood group A		Controls with blood group A		p
	Percentage (%)	Case number (positive/total)	Percentage (%)	Case number (positive/total)	
Male gender	35.1	33/94	30.0	9/30	0.607
Smoking	54.3	51/94	23.3	7/30	**0.003**
Obesity	35.1	33/94	10.0	3/30	**0.008**
Regular alcohol consumption	11.7	11/94	3.3	1/30	0.29
Dyslipidaemia	70.2	66/94	13.3	4/30	**<0.001**
Hypertension	92.6	87/94	56.7	17/30	**<0.001**
Diabetes	43.6	41/94	16.7	5/30	**0.008**
Vascular disease	71.3	67/94	13.3	4/30	**<0.001**

Table 5. Comparison between patients and control group members with blood group A

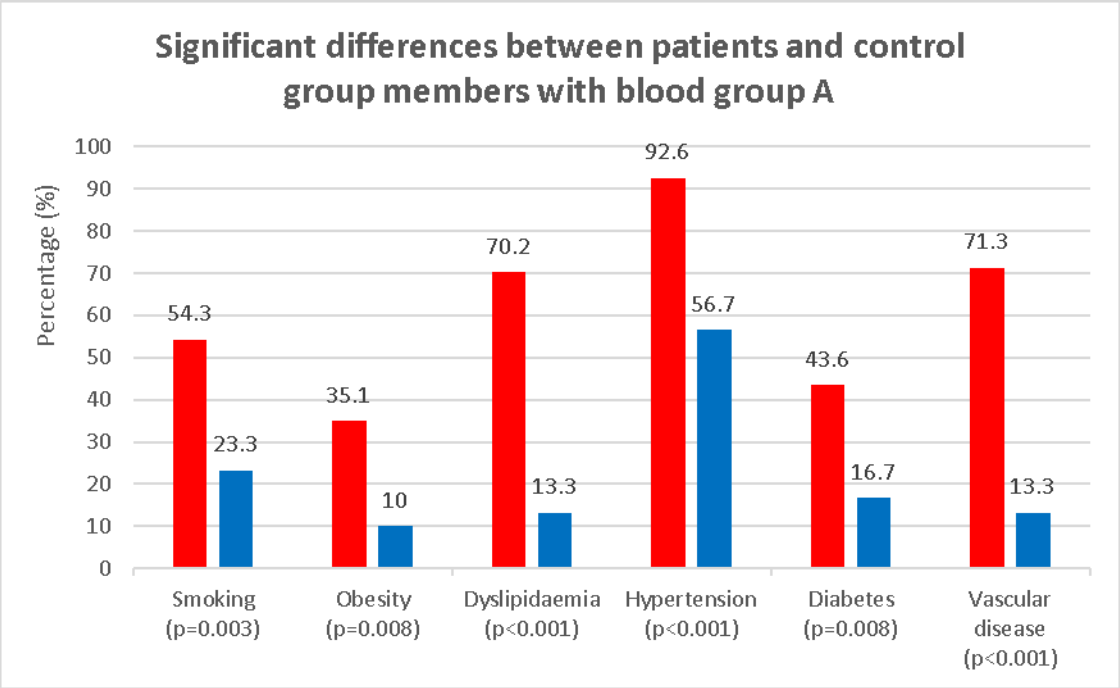


Figure 25. Significant differences between patients and control group members with blood group A

The comparison results of patients with blood group 0, B or AB and control group members with blood group 0, B or AB are summarized by Table 6. Smoking (20.4%), dyslipidaemia (20.4%) and vascular diseases (7.4%) occurred significantly less frequently among control group members with blood groups 0, B or AB than among patients with blood group 0, B or AB. Parameters with significant differences between the two subgroups are summarized by Figure 26.

	Patients with blood group 0, B and AB		Controls with blood group 0, B and AB		p
	Percentage (%)	Case number (positive/total)	Percentage (%)	Case number (positive/total)	
Male gender	37.0	30/81	38.9	21/54	0.828
Smoking	59.3	48/81	20.4	11/54	<0.001
Obesity	28.4	23/81	25.9	14/54	0.753
Regular alcohol consumption	14.8	12/81	13.0	7/54	0.762
Dyslipidaemia	64.2	52/81	20.4	11/54	<0.001
Hypertension	86.4	70/81	75.9	41/54	0.118
Diabetes	33.3	27/81	35.2	19/54	0.824
Vascular disease	56.8	46/81	7.4	4/54	<0.001

Table 6. Comparison between patients and control group members with blood group 0, B and AB

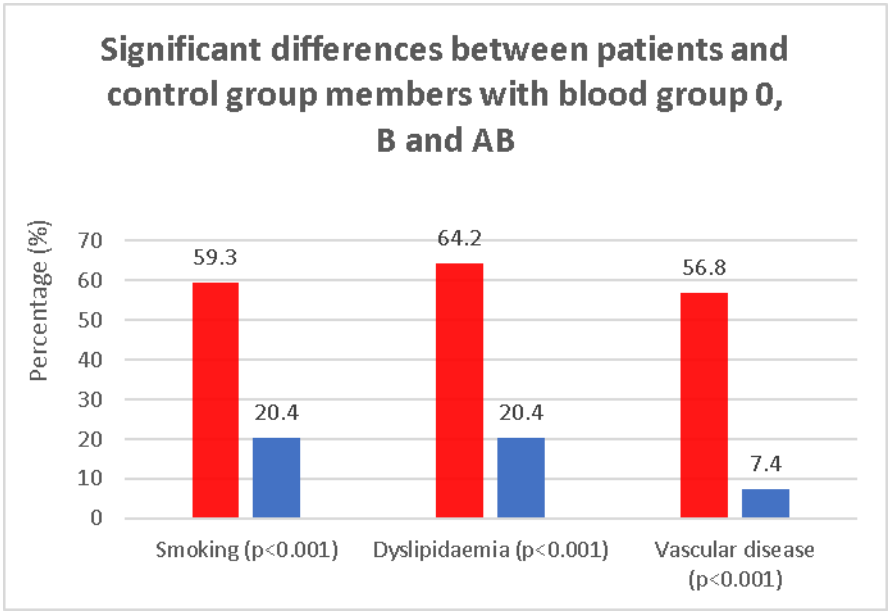


Figure 26. Significant differences between patients and control group members with blood group 0, B and AB

Further analyses

For a thorough and valid analysis, we performed the comparison on the frequency of all blood groups and allele A and B in the patient and control groups. No statistical significance was found between patient and control groups in the case of blood group 0 (36.6% in the patient group, 39.3% in the control group; p=0,683), blood group B (8.0% in the patient group, 13.1% in the control group; p=0,260) and allele A (55.4% in the patient group, 47.6% in the control group; p=0,288).

Nevertheless, blood group AB and allele B occurred less frequently in the patient group than in the control group. Among the 175 patients 3 (1.7%) had blood group AB and 172 (98.3%) had blood group 0, A or B. From the 84 people in the control group 10 (11.9%) had blood group AB, whereas 74 (88.1%) had blood group 0, A or B. As Figure 27 demonstrates, blood group AB occurred significantly less frequently in the patient group than in the control group ($p < 0.001$). Unfortunately, detailed analysis on the occurrence of different risk factors within the above-mentioned subgroups could not be performed due to the extreme low number of patients with blood group AB.

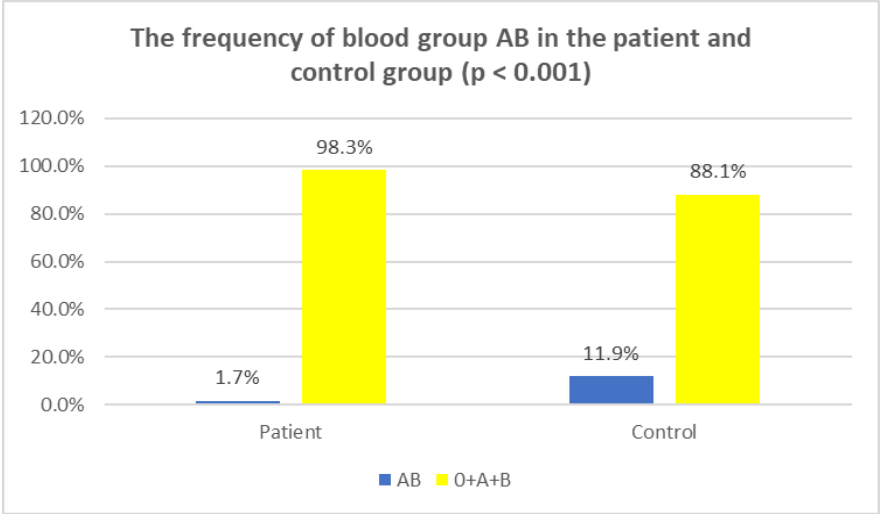
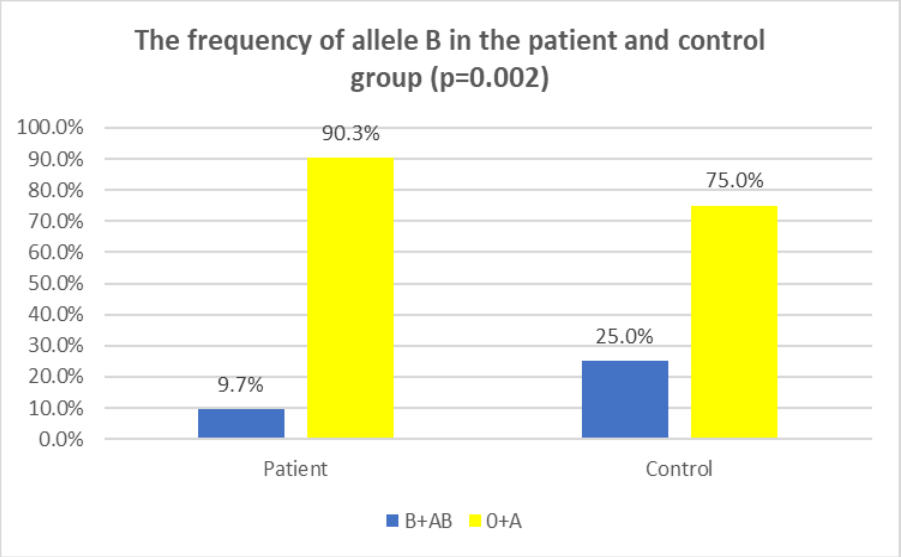


Figure 27. The frequency of blood group AB in the patient and control groups

Among the 175 patients 17 (9.7%) had allele B (blood group B and AB) and 158 (90.3%) had no allele B (blood group 0 or A). From the 84 individuals in the control group 21 (25.0%) had allele B, while 63 (75.0%) had no allele B. Figure 28 represents that allele B occurred significantly less frequently in the patient group than in the control group (p=0.002).



28. Figure. The frequency of allele B in the patient and control groups

The comparison of patients with and without allele B by gender, smoking, alcohol consumption, obesity, hypertension, diabetes mellitus, dyslipidaemia and vascular diseases revealed no significant difference, as Table 7 represents.

	B; AB patient		0; A patient		p
	Percentage (%)	Case number (positive/total)	Percentage (%)	Case number (positive/total)	
Male gender	31.3	5/16	36.7	58/158	0.789
Smoking	68.8	11/16	56.4	88/156	0.431
Obesity	33.3	5/16	32.7	51/156	1
Regular alcohol consumption	25.0	4/16	12.2	19/156	0.236
Hypertension	81.3	13/16	91.1	144/158	0.194
Diabetes mellitus	40.0	6/15	39.2	62/158	1
Dyslipidaemia	68.8	11/16	67.7	107/158	1
Vascular disease	56.3	9/16	66.2	104/157	0.422

Table 7. Comparison between patients with and without allele B

The results of the comparison between control group members with and without allele B are summarized by Table 8. Smoking occurred more frequently among control group members with allele B than those without allele B.

	B; AB control		0; A control		
	Percentage (%)	Case number (positive/total)	Percentage (%)	Case number (positive/total)	p
Male gender	38.1	8/21	34.9	22/62	0.798
Smoking	61.5	8/13	27.8	10/36	0.045
Obesity	37.5	6/16	22.9	11/48	0.329
Regular alcohol consumption	33.3	3/9	15.2	5/33	0.336
Dyslipdaemia	28.6	6/21	14.3	9/63	0.188
Hypertension	81.0	17/21	65.1	41/63	0.275
Diabetes mellitus	38.1	8/21	25.4	16/63	0.403
	14.3	3/21	7.9	5/63	0.406

Table 8. Comparison between control group members with and without allele B

The comparison results of patients and control group members with allele B are summarized by Table 9. Hypertension (28.6%) and vascular diseases (14.3%) occurred significantly less frequently among control group members with allele B than among patients with allele B (68.8%, p=0.022 and 56.3%, p=0.012, respectively).

	B; AB patient		B; AB control		p
	Percentage (%)	Case number (positive/total)	Percentage (%)	Case number (positive/total)	
Male gender	31.3	5/16	38.1	8/21	0.739
Smoking	68.8	11/16	61.5	8/13	0.714
Obesity	33.3	5/15	37.5	6/16	1
Regular alcohol consumption	25	4/16	33.3	3/9	0.673
Hypertension	68.8	11/16	28.6	6/21	0.022
Diabetes mellitus	81.3	13/16	81	17/21	1
Dyslipidaemia	4	6/15	38.1	8/21	1
Vascular disease	56.3	9/16	14.3	3/21	0.012

Table 9. Comparison between patients and control group members with allele B

As Table 10 summarizes, smoking (27.8%), dyslipidaemia (14.3%), hypertension (65.1%) and vascular diseases (7.9%) occurred significantly less frequently among control group members without allele B than among patients without allele B (46.8%, p=0.043; 67.7%, p<0.001; 91.1%, p<0.001 and 66.2%, p<0.001).

	0; A patient		0; A control		p
	Percentage (%)	Case number (positive/total)	Percentage (%)	Case number (positive/total)	
Male gender	36.7	58/158	34.9	22/63	0.877
Smoking	46.8	88/108	27.8	10/36	0.043
Obesity	32.7	51/156	22.9	11/48	0.215
Regular alcohol consumption	12.2	19/156	15.2	5/33	0.577
Dyslipidaemia	67.7	107/158	14.3	9/63	<0.001
Hypertension	91.1	144/158	65.1	41/63	<0.001
Diabetes mellitus	39.2	62/158	25.4	16/63	0.062
Vascular disease	66.2	104/157	7.9	5/63	<0.001

Table 10. Comparison between patients and control group members without allele B

Discussion

Numerous studies have suggested an association between AB0 blood groups and cardiovascular diseases, particularly with acute cardiovascular events [96-105]. The lower frequency of blood group B among patients with coronary heart disease may indicate an antiatherogenic effect of blood group B [98, 102]. A meta-analysis established that the risk by age group to develop coronary heart disease is higher among patients with non-0 blood groups [102].

More studies discussed the relationship between atherosclerotic disorders, stable coronary heart disease and AB0 blood groups [110, 111]. The examination of more than 70 000 pregnant and postpartum women revealed that venous thromboembolism develops 2-2.5x more frequently among women with blood group A or AB than among women with blood group 0 or B [112]. The combination of blood group A, B or AB and Lewis (a-, b-) phenotype leads to an increased risk of developing atherotrombotic diseases [113]. The Framingham study confirmed the elevated cardiovascular risk due to blood group non-0 [114]. A British study found close relationship between increased cardiovascular risk, blood group A and ischemic heart disease [115]. According to a Japanese study blood group A is frequently associated with elevated cholesterol level [116]. More studies confirmed a relative protective effect of blood group 0 against myocardial infarction [96, 98-99] presumably due to 01 allele based on a recent study [96]. Another study found that the presence of B allele increases the chance to develop myocardial infarction by 2.5 times [117]. A meta-analysis established that patients with blood group 0 are at lower risk to develop cardiovascular diseases than patients with other blood groups [118].

By contrast, a comparative study found no association between the severity of atherosclerosis and AB0 blood groups in Croatian patients with chronic coronary heart disease. Besides, this study revealed no significant difference in the prevalence of AB0 blood groups between patients with coronary heart disease and healthy blood donors [111]. The results of Mitchelli et al. also contradict the formerly mentioned results, according to which cardiovascular diseases more frequently lead to death among patients with blood group 0 than among patients with other blood groups, and raised the idea that the geographic differences in AB0 blood group distribution could explain the geographic differences in cardiovascular diseases [119]. Some further studies did not find any

relationship between AB0 blood groups and the development of cardiovascular diseases [101, 103].

A Lithuanian study observed more frequent occurrence of blood group B among women with coronary atherosclerosis [105]. Another study revealed significant association between blood group non-0, cardiovascular disease running in the family and elevated cholesterol level, furthermore, it confirmed more frequent occurrence of low HDL-level – a risk factor of cardiovascular risk stratification- among patients with blood group B.

The aim of our study was to confirm the more times internationally registered, however, not yet with Hungarian data demonstrated observation that blood group A occurs more frequently among patients requiring intervention surgery or heart surgery after acute cardiovascular event than among patients without acute cardiovascular event in their history. Our results confirmed this hypothesis, as the comparison of subgroups considered homogenous (adjusted for age, gender and cardiovascular risk factors including obesity, smoking, regular alcohol consumption, hypertension, diabetes and dyslipidaemia) revealed that blood group A occurs more frequently among patients requiring intervention surgery or heart surgery due to acute cardiovascular event than among patients without acute cardiovascular events in their history, even in the absence of other risk factors. The more frequent occurrence of vascular diseases in patients with blood group A than patients with blood group 0, B or AB can be considered as another manifestation of cardiovascular diseases. The comparison of patient and control subgroups with blood group A and patient and control subgroups with blood group 0, B or AB has confirmed the importance of certain traditional risk factors playing an essential role in cardiovascular risk stratification including obesity, dyslipidaemia and vascular diseases (as non-independent risk factor). However, it is important to note that the difference between patient and control subgroups in the frequency of traditional cardiovascular risk factors was far more pronounced in the case of blood group A, moreover, only in this group was a significant difference between patient and control subgroups in the case of certain cardiovascular risk factors including obesity, hypertension and diabetes detected.

Further analyses – based on the comparison of homogenous groups adjusted by age, gender and cardiovascular risk factors including obesity, smoking, regular alcohol consumption, hypertension, diabetes and dyslipidaemia – revealed that blood group AB

and allele B occurred much less frequently in the Hungarian population among patients underwent intervention surgery or heart surgery after an acute cardiovascular event than control group members without acute cardiovascular event in their history. The comparison of patient and control subgroups with and without allele B showed that whereas in the case of individuals without allele B the difference between smoking, dyslipidaemia and hypertension could emphasize their role in cardiovascular risk estimation, in the presence of allele B, only in the case of hypertension was a significant difference evaluated. This finding is underlined by an additional fact, namely that smoking occurred significantly more frequently among control group members with allele B than those without allele B, suggesting an uncommon scientific question, whether traditional risk factors can equivalently be utilized in cardiovascular risk estimation, or their utilization should be modified by the AB0 blood group. It must be mentioned though, that the relatively low number of patients and control group members with allele B (17 and 21, respectively) could – by low chance – have a distorting effect on the statistical analysis.

Further studies are required to determine individual risk factors associated with different blood groups, nonetheless, the integration of this factor to cardiovascular risk stratification could further refine that.

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PUBLICATIONS

Articles and abstracts related to the thesis

- Mrekváné BZ; SándorB, Petrus I, Verzár Z. Az AB0 vércsoport, mint kardiovaszkuláris rizikófaktor. EGÉSZSÉG-AKADÉMIA 11: 1-2 pp. 19-29, 11 p. (2020)

- Mrekváné BZ, Pakai A, Cziráki A, Verzár Z. Novel Aspects of Differences in Arterial Stiffness Parameters during Short Abstinent Period in Smokers vs. Non-smokers. Artery Research 26: (4) pp. 212-218.

- Mrekváné BZ, Pakai A, Prémusz V, Horváth L, Madarász I, Oláh A, Boncz I, Verzár Z. AB0 Blood Groups As Cardiovascular Risk Factors: A Case Control Study. VALUE IN HEALTH (1098-3015 1524-4733): 23 Suppl 2 pp S504-S504 (2020).

NEW FINDINGS

- We provide a 24-h database of arterial stiffness parameters including pulse wave velocity, central and brachial augmentation index and central systolic blood pressure on both non-smokers and smokers.
- The differences in daytime and daily heart rate between non-smokers, smokers on the non-smoking day and smokers on the smoking day are likely to reflect an improper heart rate adaptation of smokers to everyday activities.
- Pulse wave velocity is the most sensitive tested arterial stiffness parameter to smoking.
- The physiological circadian rhythm of cardiovascular and arterial stiffness parameters appears to be diminished in smokers.
- Blood group A occurs more frequently in an age- and sex-matched, homogenous Hungarian population among patients requiring intervention surgery or heart surgery due to an acute cardiovascular event than among patients without cardiovascular event in their history, even in the absence of other risk factors.
- Considering the comparison of patient and control subgroups with the same blood group, significant occurrence in obesity, hypertension and diabetes can only be observed in the case of blood group A.
- Blood group AB and allele B occurred less frequently in an age- and sex-matched, homogenous Hungarian population among patients underwent intervention surgery or heart surgery due to an acute cardiovascular event than among patients without cardiovascular event in their history, even in the absence of other risk factors.

List of abbreviations

ABPM – ambulatory blood pressure monitoring

AIX – augmentation index

AIX_{br} – brachial augmentation index

AIX_{ao} – aortic/central augmentation index

CVD – cardiovascular disease

baPWV – brachial-ankle pulse wave velocity

BMI – body mass index

brPWV – brachial-radial pulse wave velocity

cfPWV – carotid-femoral pulse wave velocity

crPWV – carotid-radial pulse wave velocity

CRP – C-reactive protein

DBP – diastolic blood pressure

DBP_{br} – brachial diastolic blood pressure

EU – European Union

HDL – high density lipoprotein

HR – heart rate

LDL – low density lipoprotein

MAP – mean arterial pressure

NSTEMI – non-ST-elevation myocardial infarction

PP – pulse pressure

PWV_{ao} – aortic/central pulse wave velocity

RT – return time

RTD – respiratory tract disease

SBP – systolic blood pressure

SBP_{ao} – aortic/central systolic blood pressure

SBP_{br} – brachial systolic blood pressure

VO_{2max} – maximal oxygen consumption

TABLE OF CONTENTS

LIST OF FIGURES

7. sz. melléklet

DOKTORI ÉRTEKEZÉS BENYÚJTÁSA ÉS NYILATKOZAT A DOLGOZAT EREDETISÉGÉRŐL

Alulírott

név: Mrekváné dr. Burián Zsófia Valéria

születési név: Burián Zsófia Valéria

anyja neve: Bíbor Marianna Erzsébet

születési hely, idő: Pécs, 1986.04.26.

The effect of different extrinsic and intrinsic factors on the cardiovascular system

című doktori értekezésemet a mai napon benyújtom a(z)

Egészségtudományi Doktori Iskola

Kardiovaszkuláris egészségtudomány (PR-2) Programjához/témacsoportjához

Témavezető(k) neve: Prof. Dr. Verzár Zsófia, Karamánné dr. habil. Pakai Annamária

Egyúttal nyilatkozom, hogy jelen eljárás során benyújtott doktori értekezésemet
- korábban más doktori iskolába (sem hazai, sem külföldi egyetemen) nem nyújtottam be,
- fokozatszerzési eljárásra jelentkezésemet két éven belül nem utasították el,
- az elmúlt két esztendőben nem volt sikertelen doktori eljárásom,
- öt éven belül doktori fokozatom visszavonására nem került sor,
- értekezésem önálló munka, más szellemi alkotását sajátomként nem mutattam be, az irodalmi hivatkozások egyértelműek és teljesek, az értekezés elkészítésénél hamis vagy hamisított adatokat nem használtam.

Dátum: Pécs, 2023. január 3.

.....
doktorjelölt aláírása

.....
Prof. dr. Verzár Zsófia
témavezető aláírása

.....
Karamánné dr. habil Pakai Annamária
társtémavezető aláírása