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

Doctoral (Ph.D.) thesis

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INTRODUCTION

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: chronic ischemic heart diseases are currently the most frequent cause of death among cardiovascular diseases. This disease group represents an outstanding economic burden of 210 billion Euros on the European Union. The management of atherosclerosis as the 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 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 (SBPao). Indirect, oscillometric values of these parameters represent a clear and apparent correlation with direct, invasively obtained values.

AIMS

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 the potential variation of the diurnal profile in smokers. The **third study** intended to assess the effect of AB0 blood groups on the cardiovascular risk.

The following scientific questions were planned to be answered with the studies:

1. What is the effect of smoking cessation on hemodynamic and arterial stiffness parameters during the first 24 hours?
2. Can a diurnal variation be recognized in 24-hour arterial stiffness parameters?
3. If a diurnal variation is present, does it correlate with former observations?
4. Is there a diurnal variation in the 24-hour arterial stiffness parameters of smokers?
5. Have AB0 blood groups an influence on cardiovascular risk?

MATERIALS AND METHODS

A common database was created for the **first and the second study** based on the results of the common test and control groups. This common database was analysed according to various aspects. The test group consisted of ten healthy light smokers, who were ordered to abstain from cigarette smoking during the first 24 hours (”non-smoking day”) and were allowed to smoke and expected to smoke at least 10 cigarettes during the second 24 hours (”smoking day”). The control group consisted of ten healthy non-smokers. Waking and sleep periods were adjusted individually with the following measurement rate: brachial systolic and diastolic pressure (SBP_{br}, DBP_{br}), heart rate (HR) and arterial pulse pressure waveform were measured, aortic systolic blood pressure (SBP_{ao}), aortic augmentation index (AIX_{ao}), brachial augmentation index (AIX_{br}) and aortic pulse wave velocity (PWV) were derived, whereas pulse pressure (PP) and mean arterial pressure (MAP) were calculated in every 20 minutes during waking hours, in every 15 minutes for a 4-hour-long period after waking up and in every 40 minutes during sleeping hours.

As demonstrated in Figure 1, augmentation index (AIX) was calculated as the difference of the reflected (second, backward, P2) and ejected (first, forward, P1) peaks of the central pulse pressure waveform expressed as a percentage of the pulse pressure. Pulse wave velocity was calculated as the jugulum-symphysis distance – estimating the aortic length with a satisfactory degree – divided by the half of the return time (RT).

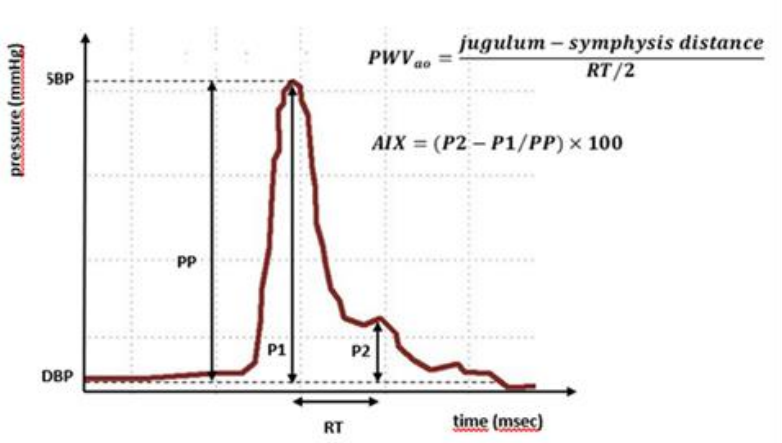


Figure 1. Calculation methods of pulse wave value and augmentation index from the pulse pressure waveform

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

All participants abstained from alcohol containing beverages and physical exertion (e.g. sport activities) outside usual daily activities. Exclusion criteria included any chronic diseases possibly affecting cardiovascular function, as well as regular alcohol or drug consumption.

Statistical analysis was performed with IBM SPSS Statistics v22.0 software. The sample was tested for normality using the 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-samples T-test. The results of the control group and the light smoker group were compared to each other with the independent samples T-test. Significance level ≤ 0.05 was considered significant.

Waking hours were divided into 4-hour-long periods in the **second study**:

1. period: awakening – awakening + 3:59
2. period: awakening + 4:00 – awakening + 7:59
3. period: awakening + 8:00 – awakening + 11:59
4. period: awakening + 12:00 – falling asleep

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.

The study population of the **third study** consisted of 63 men and 112 women diagnosed with acute cardiovascular event and undergone surgical intervention or heart surgery at the Heart Institute at the University of Pécs. 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 medical history. Gender, age, body mass index (BMI), smoking habit, alcohol consumption, as well as the presence of dyslipidaemia, hypertension, diabetes mellitus and peripheral vascular disease were recorded.

Age comparison was performed with independent samples T-test, whereas 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 ≤ 0.05 was considered significant.

RESULTS

In the **first and the second study**, test and control population can be considered homogenous in terms of age and BMI (mean age: 29.00 ± 8.78 years and 28.90 ± 10.72 years, p=0.98; mean BMI: 22.89 ± 3.42 and 22.14 ± 2.33, p=0.57, respectively).

Figures 2.a-c 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.

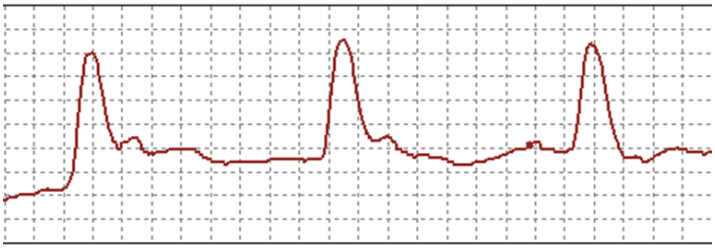


Figure 2.a

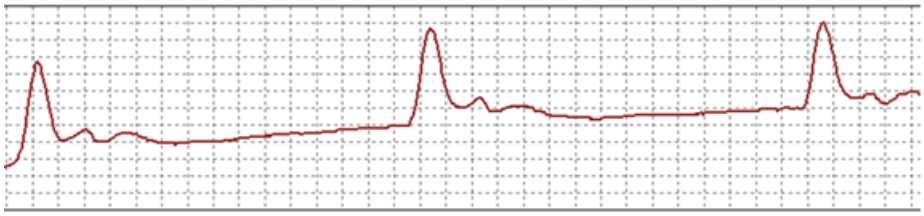


Figure 2.b

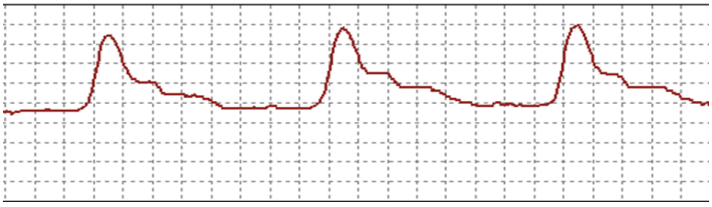


Figure 2.c

Table 1 summarizes the results of the **first study** in the non-smoking group and in the smoking group on both non-smoking and smoking days – represented as means ± standard deviations. With one exception highlighted in the text daily values of parameters changed in the same manner as daytime values.

		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
SBP_{ao} (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 table of hemodynamic and arterial stiffness parameters in different times of the day, represented as mean ± standard deviations.

As Figure 3 represents, 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).

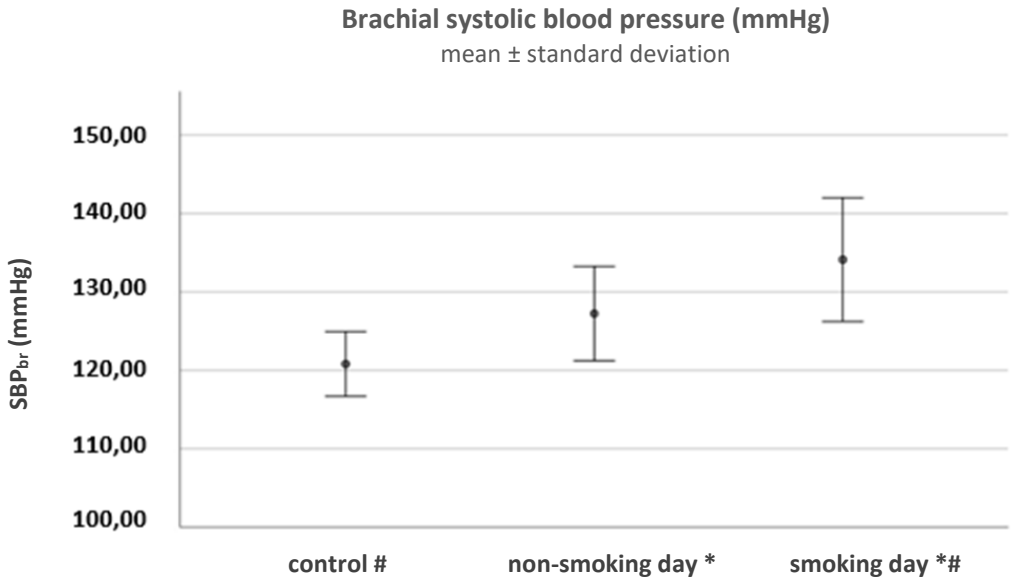


Figure 3. Brachial systolic blood pressure represented as mean ± standard deviation among non-smokers, smokers on the non-smoking day and smokers on the smoking day

* 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

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 mmHg, 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).

D*iastolic 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. 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 (p=0.36) or smokers on the smoking day and non-smokers (p=0.06).

Daily *heart rate* 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).

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). 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).

No statistical difference was revealed between daytime *pulse pressure* values of different groups; nevertheless, 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).

No statistically significant differences were revealed between *aortic systolic blood pressure*, *aortic augmentation index* and *brachial augmentation index* values during any time of the day.

As demonstrated in Figure 4, *pulse wave velocity* was significantly higher during daytime among smokers on the smoking day than on the non-smoking day (0.48 ± 0.41 m/s, p=0.03).

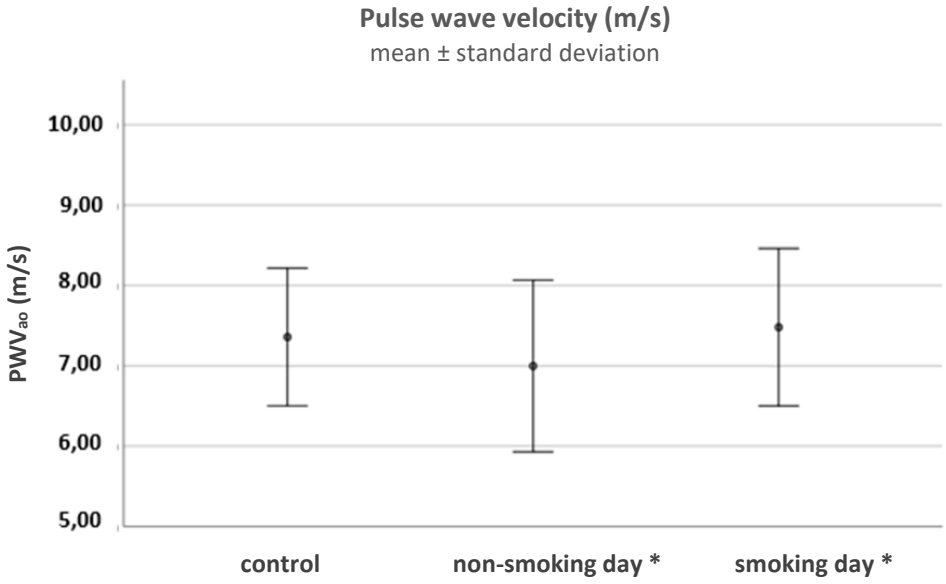


Figure 4. Pulse wave velocity values – represented as mean ± standard deviation – among non-smokers, among smokers on the non-smoking day and among smokers on the smoking day

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

Legend: PWVao: central pulse wave velocity

The results of the **second study** are represented as mean ± standard error.

As shown in Figure 5-8, *brachial systolic blood pressure*, *diastolic blood pressure* and *mean arterial pressure* were significantly higher in non-smokers during period 3 (awakening + 8 hours – awakening + 11 hours and 59 minutes) than the daily average.

	period 3	**daily average**	**p**
SBP_{br}	125.15 ± 1.72 mmHg	120.80 ± 1.82 mmHg	0.003
DBP_{br}	71.32 ± 1.92 mmHg	68.37 ± 1.54 mmHg	0.035
MAP	89.26 ± 1.50 mmHg	85.85 ± 1.43 mmHg	0.008
SBP_{ao}	114.05 ± 2.53 mmHg	111.52 ± 2.46 mmHg	0.033

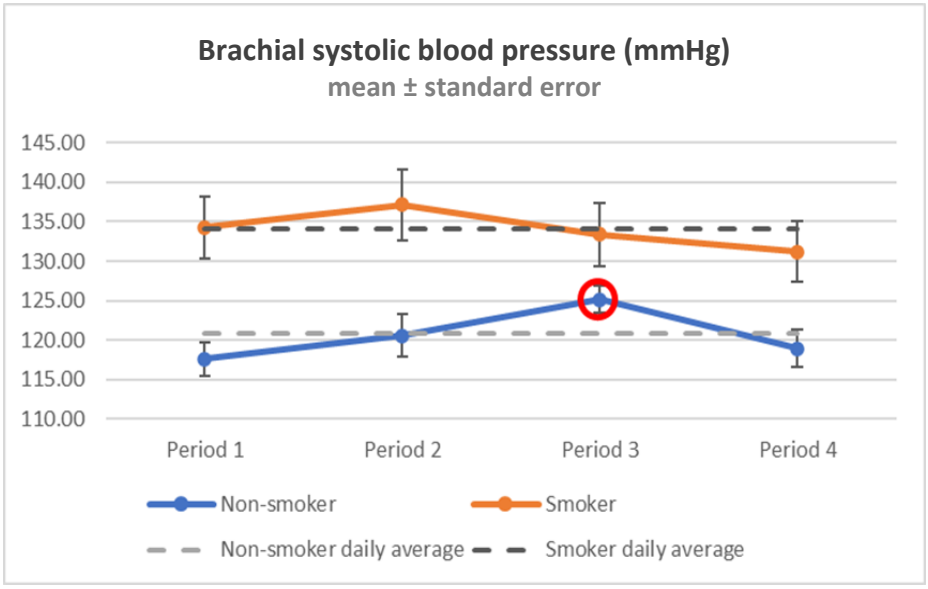


Figure 5

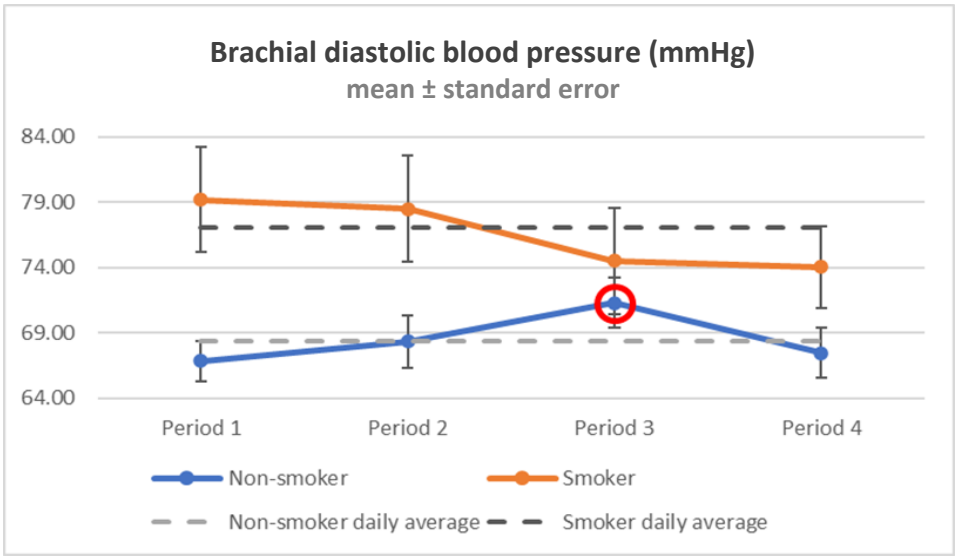


Figure 6

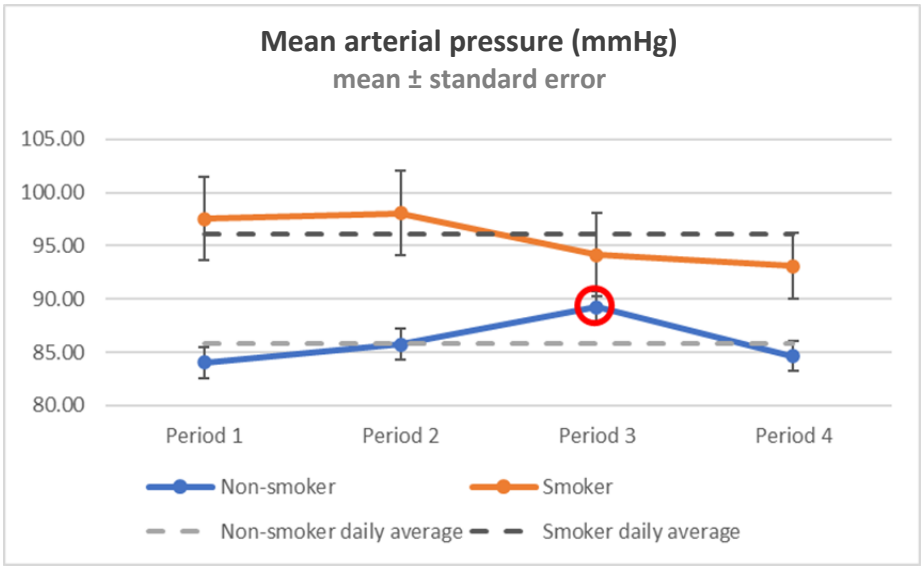


Figure 7

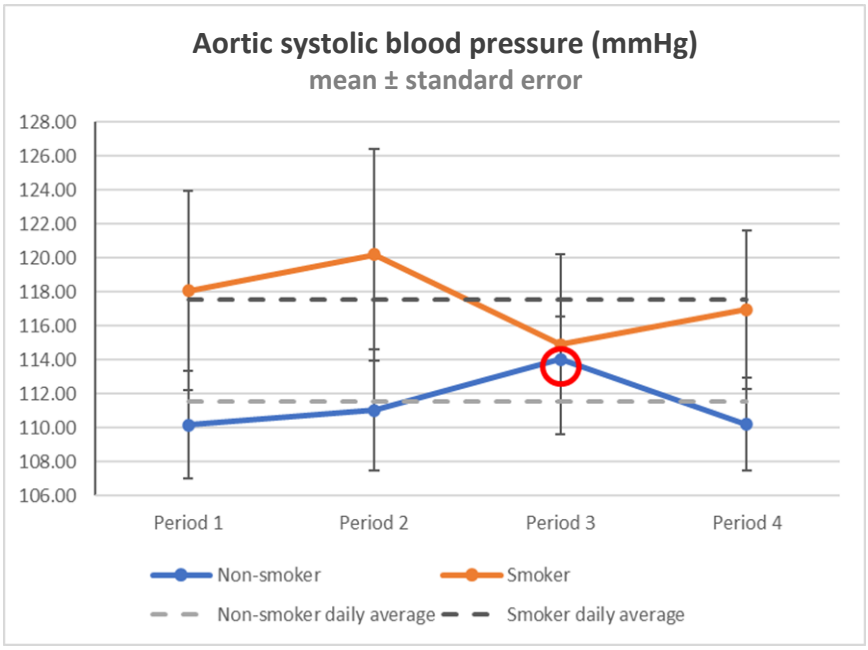


Figure 8

As Figure 9 and 10 demonstrate, *heart rate* and *pulse wave velocity* values were significantly higher in no-smokers during period 2 and period 3 than the daytime average.

	period 2	**period 3**	**daily average**	**p**
HR	77.17 ± 3.33 bpm	76.70 ± 3.03 bpm	73.80 ± 2.31 bpm	0.032
PWV	7.81 ± 0.40 m/s	7.70 ± 0.45 m/s	7.36 ± 0.37 m/s	0.022

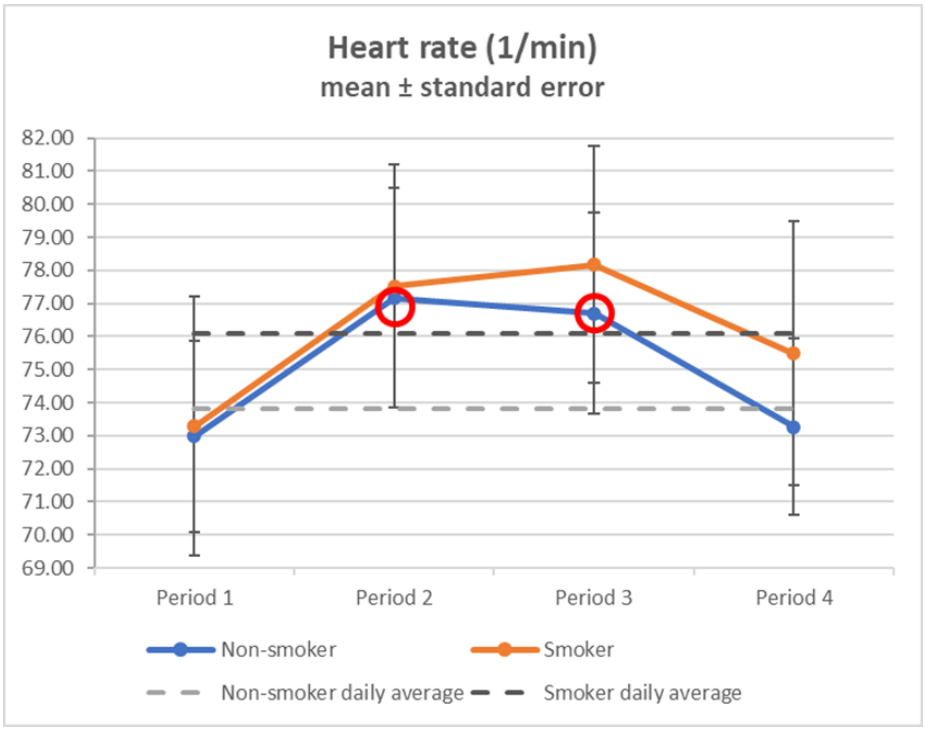


Figure 9.

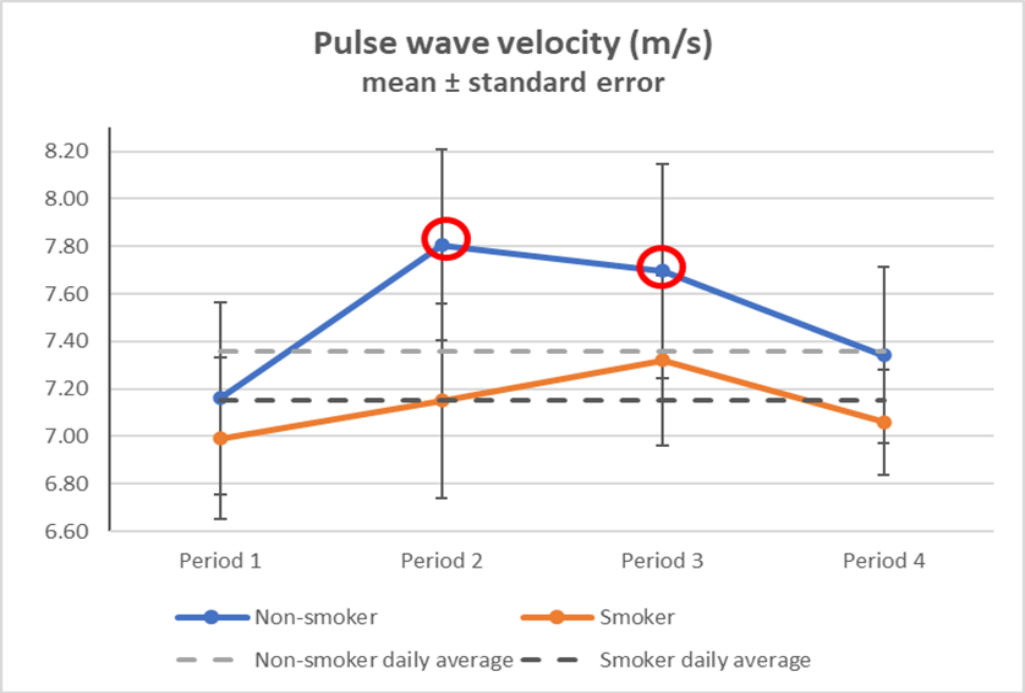


Figure 10.

Figure 11-12 represent that *central augmentation index* and *brachial augmentation index* values were significantly lower in smokers during period 3 than the daytime average.

	period 3	**daily average**	**p**
AIX_{ao}	-56.15 ± 5.81	-50.34 ± 6.58	0.002
AIX_{br}	9.21 ± 2.94	12.16 ± 3.33	0.002

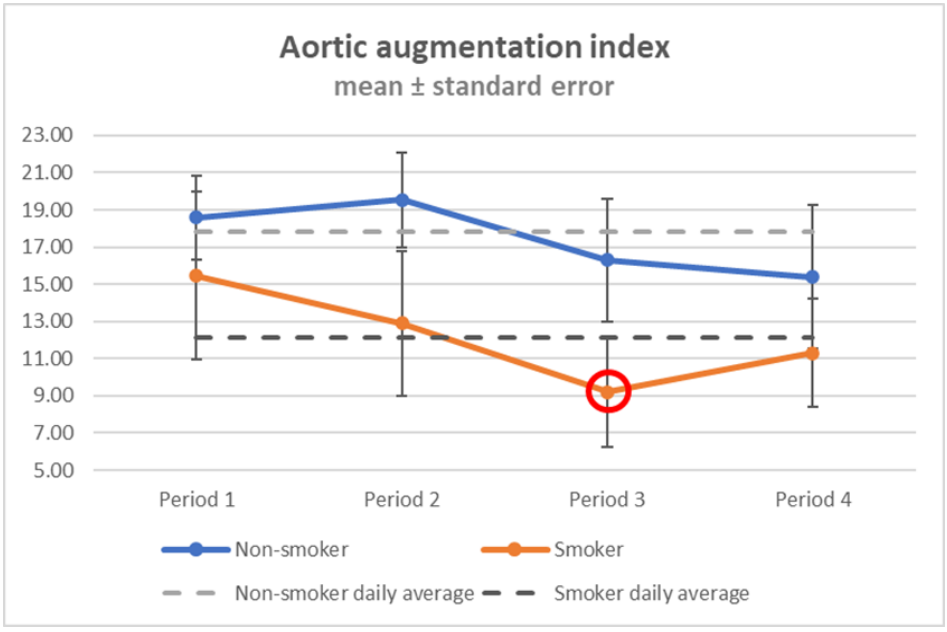
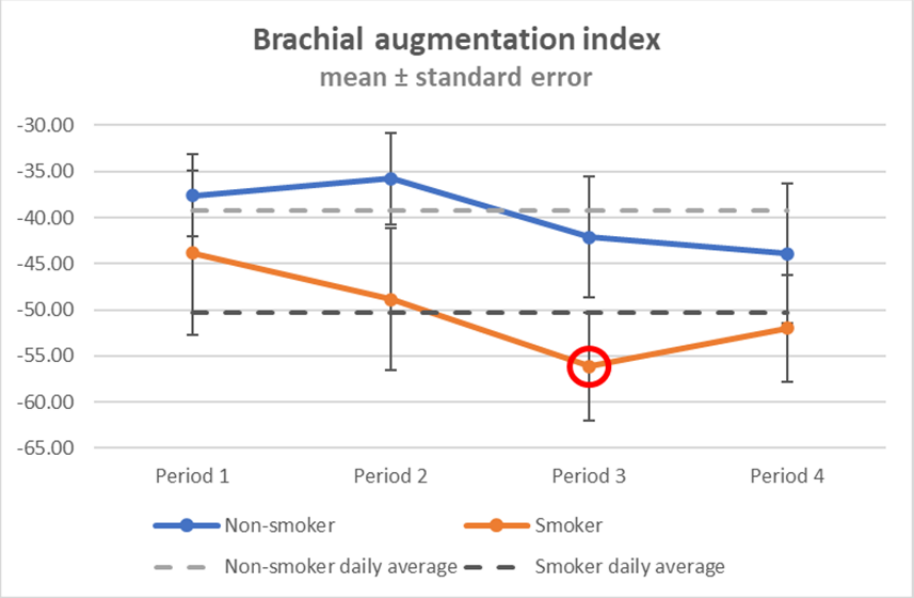


Figure 11.

Figure 12.



Apart from *central and peripheral augmentation index* values, no significant differences were identified in smokers between any time periods and the daytime average.

In the **third study**, patient and control groups were matched for age (64.74 ± 8.53 years and 65.24 ± 13.07 years, respectively, p=0.795) and gender (prevalence of men: 36.0% and 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 control group members 30 (35.7%) had blood group A and 54 (64.3%) had blood group 0, B or AB. As Figure 13 demonstrates, blood group A occurred significantly more frequently in the patient group than in the control group (p=0.007).

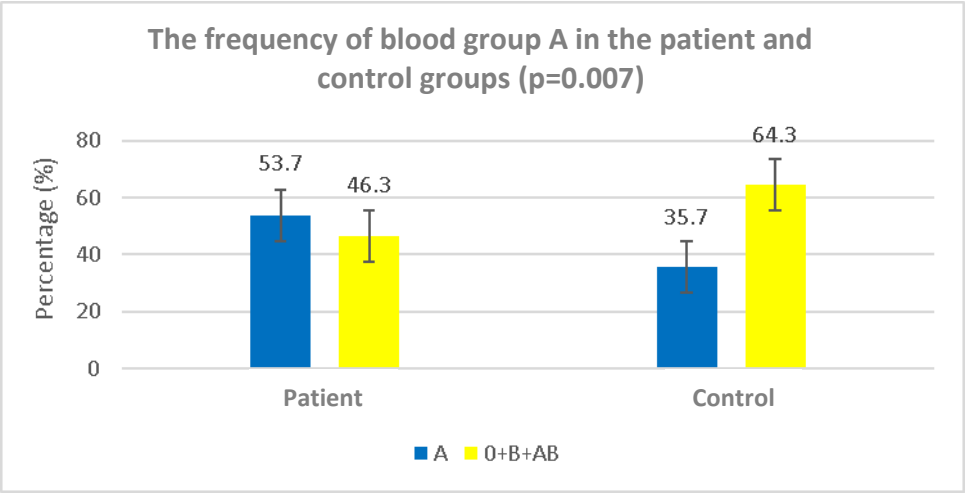


Figure 13

The comparison of *patients with blood group A and patients with blood group 0, B or AB* by gender, smoking, regular 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).

No significant differences were revealed with the comparison of *control group members with blood group 0, B or AB and control group members with blood group A*.

The comparison of *control group members and patients with blood group A* revealed that smoking, obesity, dyslipidaemia, hypertension, diabetes and vascular diseases occurred significantly less frequently among control group members with blood group A than among patients with blood group A (23.3% vs. 54.3%, p=0.003; 10.0% vs. 35.1%, p=0.008; 13.3% vs. 70.2%, p<0.001; 56.7% vs. 92.6%, p<0.001; 16.7% vs. 43.6%, p=0.008; 13.3% vs. 71.3%, p<0.001, respectively).Parameters with significant differences between the two subgroups are summarized by Figure 14.

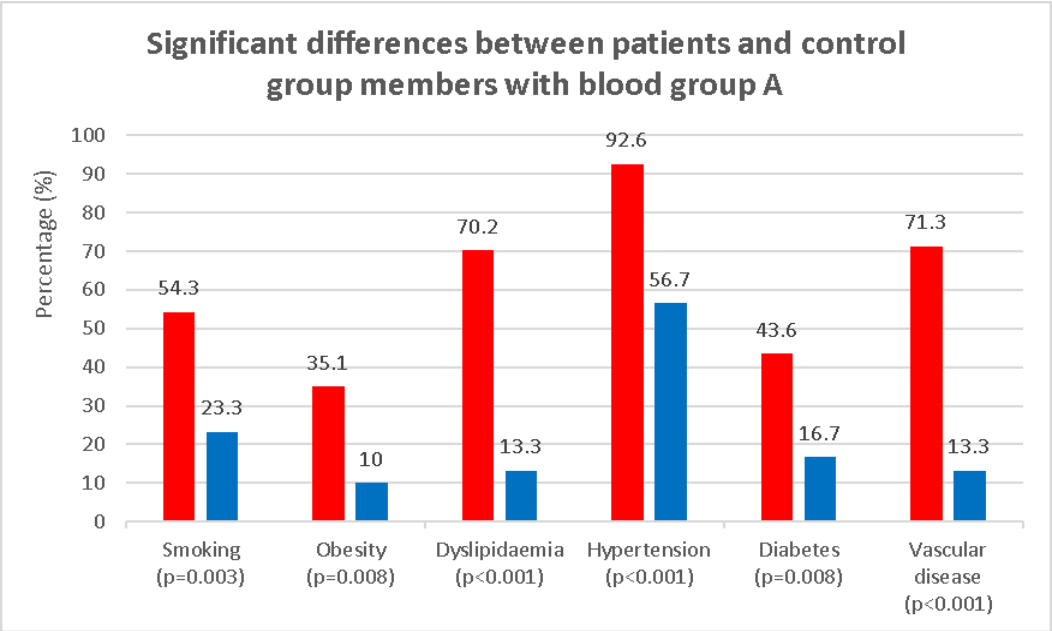


Figure 14

The comparison of *control group members and patients with blood group 0, B or AB* revealed that smoking, dyslipidaemia and vascular diseases occurred significantly less frequently among control group members with blood group 0, B or AB than among patients with blood group 0, B or AB (20.4% vs. 59.3%, p=<0.001; 20.4% vs. 64.2%, p<0.001; 7.4% vs. 56.8%, p<0.001, respectively) – as represented in Figure 15.

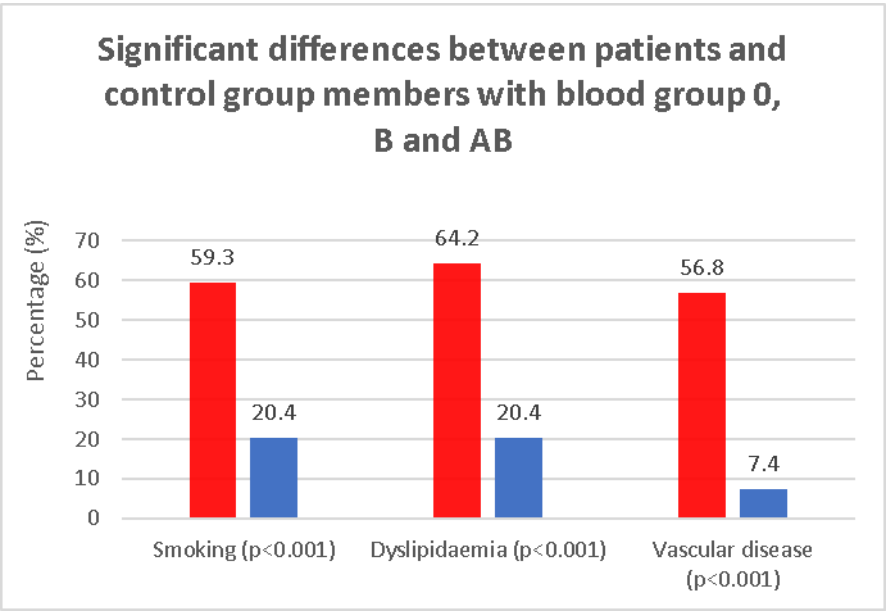


Figure 15.

For a thorough and valid analysis, we performed a comparison on the frequency of all blood groups and allele A and B in the patient and control groups revealing that – as shown in Figure 16 and 17 – *blood group B* and *allele B* occurred significantly less frequently in the patient group than in the control group (blood group AB: 1,7% vs. 11.9%, p<0.001; allele B: 9.7% vs. 25.0%, p=0.002).

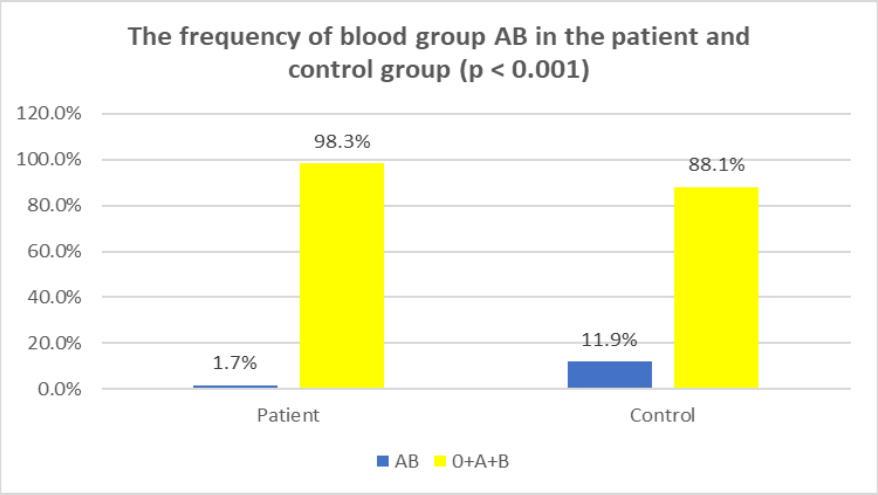


Figure 16

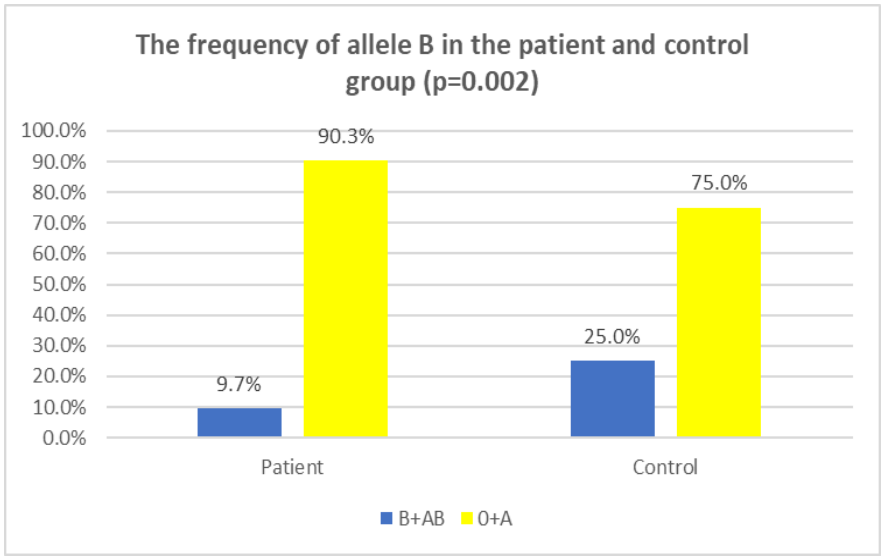


Figure 17

Detailed analysis on the occurrence of different risk factors could not be performed in the case of blood group AB due to the extreme low number of patients with blood group AB.

The comparison of *patients with and without allele B* revealed no significant difference.

The comparison of *control group members with and without allele B* resulted in one significant difference: smoking occurred more frequently among control group members with allele B (61.5%) than those without allele B (27.8%, p=0.045).

The comparison of *control group members and patients with allele B* exposed that hypertension and vascular diseases occurred significantly less frequently among control group members with allele B than among patients with allele B (28.6% vs. 68.8%, p=0.022; 14.3% vs. 56.3%, p=0.012, respectively).

The comparison of *control group members and patients without allele B* revealed that smoking, dyslipidaemia, hypertension and vascular diseases occurred significantly less frequently among control group members without allele B than among patients without allele B (27.8% vs. 46.8%, p=0.043; 14.3% vs. 67.7%, p<0.001; 65.1% vs. 91.1%, p<0.001; 7.9% vs. 66.2%, p<0.001).

DISCUSSION

In the **first study**, the highest *peripheral systolic blood pressure* value was 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 as that of non-smokers. 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.

Evaluation of the *heart rate* results of smokers alone revealed that these were consistent with previous data, the heart rate of smokers on the smoking day was 11.20 ± 5.18 bmp higher than on the non-smoking day. Interestingly, the comparison with the results of non-smokers exposed 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. The phenomenon could either be explained with an improper heart adaptation to ordinary physical activity or a secondary decrease of heart rate resulting from the decreased vascular resistance causing an increased cardiac output.

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

The analysis of daytime *pulse pressure* values revealed no statistically significant differences 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 (difference in systolic and diastolic blood pressure were 12.48 ± 7.96 mmHg and 10.14 ± 8.80 mmHg, respectively).

No statistically significant differences of *central* or *brachial augmentation index* were evaluated between the tested groups. Therefore, one day of abstinence seems to have no effect on brachial and aortic augmentation index.

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 was higher among smokers on the smoking day than on the non-smoking day, whereas no difference was found between smokers on the non-smoking day and non-smokers. 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. Pulse wave velocity appears to be the most sensitive parameter to smoking among the tested parameters.

Our **second study** revealed an obvious and significant daily peak (period 3) in *brachial systolic* and *diastolic blood pressure*, *mean arterial pressure* and *central systolic blood pressure* among non-smokers coinciding with the increased afternoon activity after work. This peak disappears among smokers resulting in a more even curve with a higher mean value, though.

The analysis of *heart rate* and *pulse wave velocity* curves revealed a double peak among non-smokers, the mean heart rate values of period 2 and period 3 were significantly higher than the daytime mean. Due to a diminished decrease of heart rate and pulse wave velocity during period 4, a more even curve formed among smokers lacking a daily peak.

The *central* and *peripheral augmentation index* curves of smokers show 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. revealing the opposite changes of systolic augmentation compared to pulse wave velocity, pressure amplification and central pressure, may assist in the resolution of this discrepancy.

The expected daily peak of every tested parameter – except central and peripheral augmentation index – diminished/disappeared in smokers. Its potential effect on cardiovascular morbidity and the timing of cardiovascular examinations is yet to be determined.

The results of the **third study** confirm a not yet on 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. The comparison of subgroups adjusted for age, gender and cardiovascular risk factors including obesity, smoking, regular alcohol consumption, hypertension, diabetes mellitus and dyslipdaemia revealed that blood group A can be considered as an independent cardiovascular risk factor, whereas allele B can be considered as an independent cardiovascular protective factor. The more frequent occurrence of vascular diseases in patients with blood group A than patients with blood group 0, B or AB is likely to

be another manifestation of atherosclerosis. Whereas significant difference was observed in the frequency of smoking, dyslipidaemia and vascular diseases in the patient and control subgroups with both blood group A and blood group 0, B and AB; obesity, hypertension and diabetes mellitus was only in the patient subgroup with blood group A significantly more frequent.

NEW FINDINGS

- A 24-h database on arterial stiffness parameters of non-smokers and smokers was published.
- The heart rate of smokers on the non-smoking day was significantly lower than that of both smokers on the smoking day and non-smokers.
- Pulse wave velocity is the most sensitive tested arterial stiffness parameter to smoking.
- Based on the evaluation of homogenous groups adjusted for age and gender, blood group A can be considered as an independent cardiovascular risk factor.
- Based on the evaluation of homogenous groups adjusted for age and gender, allele B can be considered as an independent cardiovascular protective factor.
- Considering the comparison of patient and control subgroups with the same blood group, significant difference could not be observed in the frequency of certain traditional cardiovascular risk factors in the case of certain blood groups suggesting the potential importance of integrating blood groups in cardiovascular risk stratification.

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PUBLICATIONS

Publications in the field of 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).

Other publiocations

- Zsófia Burián, Hajnalka Szabó, Gyöngyi Székely, Kálmán Gyurkovits, Péter Pankovics, Tibor Farkas, Gábor Reuter. Detection and follow-up of torque teno midi virus ("small anelloviruses") in nasopharyngeal aspirates and three other human body fluids in children. Arch Virol. 2011 Sep;156(9):1537-41.
- Pakai Annamária, Mrekváné Burián Zsófia, Shahood Hadel, Bálint Csaba, Pethőné Tóth Ibolya. Lélegeztetéssel összefüggő pneumonia kockázati tényezői – szakirodalmi áttekintés. EGÉSZSÉG-AKADÉMIA 11: 3-4 pp. 87-99., 13 p. (2020).