Genetic and environmental influences on baroreflex sensitivity and the elasticity of common carotid artery

Ph.D. thesis

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Introduction

Arterial baroreflex is a key element in the short-term blood pressure regulation. Operation of the reflex is largely dependent on the stiffness the barosensory vessel wall in which the baroreceptors are embedded. The input signal of the baroreflex is the blood pressure-induced vessel distention. When vessel distention is attenuated due to increased vascular stiffness, the efficiency of the baroreflex also decreases. Both decreased baroreflex function and increased vascular stiffness are well known independent cardiovascular risk factors.

According to the data of our own and also from international publications, it is known that both baroreflex function and arterial stiffness show a substantial intra- and inter-individual variability. This variance is driven by physiological (healthy aging, biorhythm, sex) and pathophysiological processes, however large proportion of this variance is still unexplained. In the previous decades it has been suggested, that genetic effects might influence this unknown portion of variance.

Statistics indicate that in Hungary cardiovascular morbidity and mortality are significantly higher compared to Western European countries. Whether is it purely attributed to environmental influences (absence of health conscious lifestyle, low income, low quality of foodstuffs) or the gene pool characteristic to the Hungarian people determines the development of cardiovascular disease is still debated. [1]

Aims

We aimed to determine the extent of genetic influence over *baroreflex-function* and on the *stiffness of the common carotid artery (CCA)*. Furthermore we aimed to quantify the magnitude of environmental effects with the use of classical twin studies. Since the larger influence the environment exerts on the phenotype variance, the possibility of successful preventive actions to oppose genetically coded, age-dependent deterioration of the baroreflex-function and increased vascular stiffness is also higher.

In order to quantify the relative influence of genetic and environmental effects, we have designed a classical twin study incorporating three different research methodologies. As a first step we have determined *baroreflex-sensitivity (BRS)* of the participant twin pairs. Secondly, parameters of CCA stiffness were quantified. As a third step, influences of genetic and environmental effects over the phenotypic variance and covariance were approximated, within the framework of classical twin studies.

In summary; we sought to determine the relative extent of genetic and environmental influences over the baroreflex function and CCA stiffness within a sample of Hungarian twin pairs.

Methods

Subjects of our study: twin pairs

Between 2008 and 2010, one-hundred, healthy Hungarian twin pairs were involved in our study. Participants were recruited from twin gatherings, media advertisements and from the newly forming Hungarian twin registry. [2] 63% of the participant pairs were mono- (MZ) and 37% were dizygotic (DZ) twins. Ratio of women was 73% within MZ and 70% within DZ twin pairs. Exclusively, same-sex twin pairs were recruited into our study. Participants with pregnancy, diabetes, past history of myocardial infarction, acute febrile state, and alcohol consumption over 2 units/day were excluded from the study.

Determination of baroreflex-sensitivity

We have quantified BRS based on the connection between blood pressure and heart rate. BRS shows us the amount of change in cardiac cycle length (measured in ms) due to 1 mmHg blood pressure change. During the 10 minutes-long examinations, simultaneous ECG and beat-to-beat blood pressure signal were registered. Respiratory rate of the participants were dictated by a metronome at 4 seconds/cycle (0.25 Hz) rate. Cardiac cycle length was determined from the interval length between neighboring ECG R-wave peaks (RRi). Input signal of the baroreflex is characterized by blood pressure fluctuation. This fluctuation was described by systolic blood pressure values (SBP) within each cardiac cycle. Indices of BRS were calculated in time- and frequency domains based on the 10 minutes long RRi and SBP time series. Respiratory rate control was used in order to separate concomitant RRi and SBP sequences which were resulted from respiratory sinus arrhythmia on one hand, and from baroreflex-induced sequences on the other.

Time domain, sequential BRS indices (Seq+ and Seq-)

Within time domain analysis we have identified spontaneously occurring sequences in which SBP and RRi concurrently increased or decreased over three or more consecutive beats. Local BRS was calculated as a regression slope fitted on the SBP-RRi sequences. According to the literature, we have included those sequences, which showed regression coefficients (r) greater then 0.85. During the 10 minutes-long recordings, ascending (Seq+) and descending sequences (Seq-) were identified, according to their slopes of regression. Averaging of total up and down sequences resulted the overall Seq+ and Seq- values for each participant.

Frequency-domain, spectral indices (αLF and LFgain)

The 10 minutes-long RRi and SBP time series were cubic-spline interpolated at 4 Hz in order to gain sinusoidal waveforms. Power spectral densities were plotted in the form of *Welch periodograms*. Periodograms were acquired using *fast-Fourier transformations*. Three frequency bands can be distinguished on the resulted power spectra. *Very low-frequency band* (VLF) is located below 0.04 Hz, while *low-frequency band* (LF) is located between 0.04-0.15 Hz. The *high frequency band* (HF) also known as *respiratory band* is defined between 0.15-0.4 Hz. The well characterized spectral peaks around 0.25 Hz both in SBP and RRi spectra are the result of *respiratory sinus arrhythmia*. Relation between SBP and RRi spectra were analyzed independently of respiratory patterns by focusing only to the low-frequency band. When SBP and RRi cross-spectral coherence exceeded 0.5, αLF was calculated as a square root of RRi and SBP spectral moduli. LFgain is quantified as the average of the spectral transfer function within the low frequency band.

Determination of CCA elasticity

Intraluminal radial forces – generated by intra-arterial pressure – are counterbalanced by tangential forces developed within the arterial vessel wall. *Laplace-Frank law* describes the relationship between *tangential wall stress*

and intraluminal pressure. Due to the increased intraluminal pressure, radius of the vessel is increased; therefore the vessel wall material lengthens in tangential direction. This relative tangential lengthening is referred as *tangential strain*. Within the vessel wall, forces normalized by the thickness of the wall (referred as stress) are developing. In biological systems the stressstrain relationship is nonlinear and shows convexity towards strain. The slope of the stress-strain relationship is incrementally changes towards the direction of higher strain. *Elastic modulus* is defined as the slope of the graph at a given point. Since the elastic modulus displays incremental change, it is called as *incremental elastic modulus* (Einc). When larger wall stress develops due to unit change of strain, Einc is also gets bigger. Therefore Einc is a measure of vascular stiffness.

Determination of relative strain and wall stress under *in-vivo* conditions are challenging, therefore – in practice – strain is characterized by vessel distention, while stress is described by change of intraluminal pressure. Absolute change of vessel diameter due to unit change off blood pressure is referred as *compliance*. Relative change of diameter due to change of unit blood pressure is referred as *distensibility*. In contrast with elastic modulus, compliance (compliance coefficient~CC) and distensibility (distensibility coefficient~DC) are the measures of vascular elasticity. In elastic vessels unit change of blood pressure elicits larger distention (larger compliance and distensibility).

CC and DC are parameters, which largely depend on vascular geometry. However absolute and relative vascular diameter change within physiological blood pressure range is not linear. In order to circumvent this non-linearity, the logarithmic form of stiffness index β can be used.

In order to determine elasticity and stiffness of the vessel wall we have to determine the value and change of vascular geometry parameters during the cardiac cycle. We measured these parameters by a dedicated radiofrequency-based ultrasound wall tracking system (Art.Lab Esaote, the Netherlands). With this device, magnitude of the geometrical parameters can be measured with the accuracy of 23 μm. The temporal change of these parameters can

be tracked by 1.7μm/frame rate. The change of blood pressure can be monitored over superficial arteries by applanation tonometry (SphygmoCor, AtCor Medical, Sydney Australia).

The tonometer is a pen-shaped pressure sensor converting inra-arterial pressure fluctuations to electronic signals non-invasively. Using the measured geometrical and pressure values CC, DC, Einc and stiffness index β can be quantified.

Methodology of classical twin research

Twin research is an ideal tool for determination of the extent of genetic influence on phenotypic variance. Despite the fact that pedigree analyses and examination of non-twin siblings can deliver valuable information related to the impact of genetic determination and an environmental influences, twin research is far superior for separating variance components driven by genetic influences, common environmental and unique environmental effects. It is known that genetic information of monozygotic twins is identical, while DZ twins share 50% of their genome on average. Furthermore twins have a same age and their early (intra- and early extra uterine) development is influenced by identical, common environmental effects. Based on the above-mentioned facts, twin pairs are ideal subjects of research, which aims to break down phenotype variance into its components. The technique of *structured equation modeling* (SEM) can be used to separate variance components.

Our SEM model is based on the following assumptions:

- Under ideal conditions, variances of the first born and second born twin siblings are identical. This assumption might be violated when unique environmental effects are extremely strong or the existence of non-systematic measurement errors distorts the data. In my thesis, the variance of the particular phenotype (BRS or CCA stiffness) is marked with P. Since every phenotype within the scope of this work depended on age and sex, these confounders were adjusted prior the statistical calculations were carried out.

- The within pair (between twin siblings) phenotype similarities were quantified by their covariance. Covariances normalized by standard deviations resulting correlations (rMZ monozygotic correlation, rDZ-dizygotic correlation).

- Strong intra-pair correlations can be measured when the genetic and/or the common environmental effects gaining strength.

- The diminished intra-pair correlations are the result of strong unique environmental impact or the attenuation of genetic effects over the phenotype variance.

- Variance and covariance can be separated into three components by structural equation modeling. The following three components are distinguished: *additive genetic effects* (A), *common environmental effects* (C) and *unique environmental effects* (E). Since the genome of MZ twins are 100% identical and the DZ twins share 50% of their genetic material, the additive genetic components having a correlation of 1 (100%) within MZ pairs, while the genetic correlation is 0.5 (50%) for the DZ twins. Regardless of zygosity, common environmental correlation is 1.

- There is no correlation between unique environmental influences within pairs, since these effects are influencing the siblings individually.

In summary: phenotype difference within twin pairs (proportion of the variance which is not shared siblings) can come from two sources; unique environmental influences on one hand and reduced genetic impact (mainly among DZ twins) on the other.

Components of our structural equation model:
The particular phenotype (P) is determined by the relative strengths of A, C and E latent variables (marked as a, c and e):

$$P = a^2 + c^2 + e^2$$

Intra-pair correlation equations for MZ and DZ twins:

$$rMZ = 1 \times a^2 + c^2$$

$$rDZ = 0,5 \times a^2 + c^2$$

Following rearrangement:

$$a^2 = 2 \times (rMZ - rDZ)$$

$$c^2 = 2 \times rDZ - rMZ$$

$$e^2 = P - rMZ$$

Maximum likelihood estimation (MLE) was used to fit measurement data with the previously described SEM model after employing a 1000× *bootstrap re-sampling* with replacement.

Of the particular phenotype, mean and standard deviation, along with intra-pair correlations and ACE correlation-separation was carried out by MLE.

The bootstrapped variance and variance components (A, C and E) are showing χ^2 distribution. Therefore model estimations and raw data were fitted with χ^2 tests. Good model fit can be described with non-significant test results. Significant χ^2 test p values are indicators of significant model misfit. Models with no significant test results were accepted only.

During our analyses, demographic parameters determined first. As a second step, within pair correlations were calculated. Then the correlations were separated into their A, C and E components. Besides the fully-fledged ACE models, further, partial models were constructed. The reduced AE model excluded common environmental effects, while the CE model neglected genetic influences. We have analyzed the possibility whether these partial models might fit as well as the full ACE model. In case the partial model showed a good fit to real world data then the partial model was chosen for publication. In case when we were not able to exclude any (or both) partial models – according to conventions – the full ACE model was chosen for publication.

Results

Demographic data

Results of demographic analyses are shown in table 1. Ratio of the participating MZ and DZ pairs were ~6/4. 70% of the participants were female. On the average MZ twins were ~10 years older compared to their DZ counterparts. This age difference was measurable on both peripheral (brachial) and central (carotid) blood pressure values.

		MZ (63 pairs)		**DZ** (37 pairs)		**p**
		mean	**SD**	**mean**	**SD**	
women	[%]	73	-	70	-	0.77
age	[years]	48	15.0	37	13.7	¡0.001
BMI	$\left[\frac{kg}{m^2}\right]$	26	5.0	25	5.8	0.38
waist	[cm]	88	14.5	88	15.5	0.90
heart rate	[1/minute]	70	11.9	71	8.2	0.51
Brachial blood pressure						
SBPb	[mmHg]	131	14.6	125	13.5	0.02
DBPb	[mmHg]	74	10.1	72	9.8	0.21
PPb	[mmHg]	56	8.3	53	7.8	0.09
Carotid blood pressure						
SBPc	[mmHg]	119	14.4	114	13.2	0.05
DBPc	[mmHg]	75	10.0	72	10.0	0.30
PPc	[mmHg]	44	8.3	41	7.7	0.07

Table 1: *Cluster-corrected demographic parameters of the MZ and DZ twins. Statistics: MLE hypothesis test.*

Phenotype data

Phenotype variables describing BRS and carotid stiffness are shown in table 2. Both BRS and CCA stiffness showed age-related differences between MZ and DZ twins. In case of MZ twins BRS indices were lower ~3 ms/mmHg on average compared to DZ twins. [3] CCA elasticity parameters (CC and DC) were attenuated, while stiffness parameters (stiffness index beta and Einc) were augmented in MZ twins. Despite both BRS and CCA stiffness showed age-related deterioration, both sets of parameters were within normal range. [4]

		MZ		**DZ**		**p**
		mean	**SD**	**mean**	**SD**	
Seq+	$\left[\frac{ms}{mmHg}\right]$	11.6	8.9	14.7	10.3	0.02
Seq-	$\left[\frac{ms}{mmHg}\right]$	11.1	8.9	13.6	9.3	0.01
α**LF**	$\left[\frac{ms}{mmHg}\right]$	8.2	7.4	11.8	8.6	0.02
LFgain	$\left[\frac{ms}{mmHg}\right]$	6.6	5.6	8.1	5.3	0.02
CC	$\left[\frac{mm^2}{mmHg}\right]$	0.10	1.43	0.11	1.54	0.06
DC	$\left[\frac{10^{-3}}{mmHg}\right]$	2.95	1.50	3.56	1.51	0.03
Stiff β	[-]	9.51	4.53	8.03	5.05	0.02
Einc	[mmHg]	4.40	2.54	3.96	3.48	0.20

Table 2: *Phenotypic data of the participants. Statistics: cluster-corrected MLE hypothesis test.*

Results of intra-pair correlations

Phenotype correlations between twin pairs in their 95% confidence intervals are displayed in table 3. Without exception all the parameters showed good fit with real world data. Column p shows the p values of the χ^2 test. None of these values showed a significant misfit. For BRS phenotype, MZ and DZ correlations were almost identical. This phenomenon was developed because of the relative strengthening rDZ compared to rMZ. [3] Strengthening of rDZ might be the result of increased common environmental impact. In the case of CCA stiffness, MZ correlations were higher than DZ correlations. For all stiffness parameters rMZ were around twice as high compared with rDZ. This correlation-ratio might be due to the dominance of additive genetic effects. [4]

	rMZ	95% CI	**rDZ**	95% CI	**p**
Seq+	**0.350**	0.071 - 0.589	**0.294**	-0.013 - 0.582	0.939
Seq-	**0.301**	0.115 - 0.491	**0.284**	-0.432 - 0.664	0.524
α**LF**	**0.440**	0.184 - 0.663	**-0.085**	-0.341 - 0.280	0.230
LFgain	**0.350**	0.071 - 0.589	**0.294**	-0.013 - 0.582	0.939
CC	**0.601**	0.388 - 0.750	**0.368**	0.124 - 0.594	0.856
DC	**0.635**	0.450 - 0.768	**0.328**	-0.008 - 0.596	0.455
Stiff β	**0.580**	0.292 - 0.772	**0.190**	-0.166 - 0.527	0.206
Einc	**0.635**	0.472 - 0.768	**0.105**	-0.319 - 0.531	0.272

Table 3: *Intra-pair correlations. rMZ monozygotic correlation, rDZ dizygotic correlation; Stiff β: stiffness index β; CI: confidence interval; p: model-fit χ^2 test significance. Statistics: age and sex adjusted MLE bivariate correlation.*

Results from the full and partial ACE models

Results of ACE modeling of BRS and CCA parameters are shown in table 4. Table 4 contains only the final accepted models. Fit parameters for the full ACE and partial (AE and CE) models are shown in the first three columns. The first column indicates the χ^2 test p value (p), which resulted by comparing the correlation results (table 3) with the full ACE and the partial AE and CE models. Since the full and partial models break down intra-pair correlations to its components, it is cordial that that fit of the ACE models are acceptable. Model is considered acceptable when the p value in the first column doesn't indicate significant misfit. In contrast, the presence of significant p values results the exclusion of the given model. In the third column, p_{χ^2} values indicate whether the partial models (AE and CE) fit well to the full ACE model. In case of significant misfit ($p>0.05$) the partial model cannot be used as a substitute for the full model. After the exclusion of one of the partial models, Akaike's information criterion (second column ~AIC) enables us to choose from the remaining full and partial model. The more robust the model is, the more smaller the AIC value (good fit can be achieved by using less input parameters) will turn out. Choosing the model with smaller AIC parameter is the way to select the final solution. In case when none of the partial models can be excluded with certainty – according to conventions – the full ACE model has to be selected.

ACE models for baroreflex-indices

Based on the results of BRS indices, we were not able to select a partial model so the full ACE models were used.

In case of Seq+ 32% of the variance were driven by common environmental effects (column C), while unique environment (column E) influence could be attributed to the rest of the 68% variance. 39% of the Seq- variance was explained by genetic effects (column A). Unique environmental influences were responsible for 61% of the Seq- variance. Despite our model predicted 0 common environmental determination on average, it has to be noted

that the confidence intervals of additive genetic and common environmental influences are substantially overlapping. Genetic determination of αLF variance was 35%, while unique environmental influences predicted 65% off the remaining variability. Although common environmental effects (C effects) were part of the model, this influence could not be measured – most probably – due to the small sample size. A, C and E variance components turned out 22%, 2% and 76%, respectively for our LFgain model.

ACE models for CCA stiffness

With the exception of compliance, AE models showed to be the most parsimonious, best fitting models for all bio-mechanical indices. In the case of compliance – similarly to the BRS indices – we could not select out a proper submodel, therefore the full ACE model was used. In respect to CC variance, proportion of genetic determination was 47%, common environmental effects exerted 14% influence, while unique environment drove 40% of the phenotype variance. Genetic effects were responsible for 64% of the DC variance, 58% for stiffness index β variance and 62% for Einc variability. Since no common environmental effects could be detected for the above-mentioned three parameters, unique environmental effects determined 36%, 42%, and 38% of the phenotype variance, respectively.

	Model	p	AIC	p_{χ^2}	**A**	95% CI	**C**	95% CI	**E**	95% CI
Seq+	**ACE**	0.595	1007.972	-	**0.00**	0.00 - 0.43	**0.32**	0.00 - 0,53	**0.68**	0.50 - 0.84
Seq-	**ACE**	0.458	1037.088	-	**0.39**	0.00 - 0.72	**0.00**	0.00 - 0,49	**0.61**	0.36 - 0.79
αLF	**ACE**	0.096	480.216	-	**0.35**	0.07 - 0.62	**0.00**	0.00 - 0,00	**0.65**	0.38 - 0.92
LFgain	**ACE**	0.993	1125.696	-	**0.22**	0.00 - 0.59	**0.02**	0.00 - 0,41	**0.76**	0.49 - 0.99
CC	**ACE**	0.856	-834.258	-	**0.47**	0.00 - 0.73	**0.14**	0.00 - 0,53	**0.40**	0.25 - 0.60
DC	**AE**	0.537	542.807	0,950	**0.64**	0.47 - 0.77	-	-	**0.36**	0.23 - 0.53
Stiffβ	**AE**	0.253	51.591	1,000	**0.58**	0.30 - 0.77	-	-	**0.42**	0.23 - 0.69
Einc	**AE**	0.251	157.233	1,000	**0.62**	0.46 - 0.77	-	-	**0.38**	0.23 - 0.54

Table 4: *Age and sex corrected ACE models. p: model fit test p value; AIC: Akaike's informational criterion; p_{χ^2}: partial model fit information related to the full ACE model; A: additive genetic influences; C: common environmental influences; E: unique environmental influences; CI: confidence interval*

Conclusions

Based on a cohort of 100 healthy twin pairs we have determined the relative influence of genetic and environmental effects on baroreflex-function and on CCA stiffness, which is considered as a main determinant of the reflex.

In relation of BRS indices, correlation within MZ and DZ twin pairs turned out to be nearly similar. Although the correlation within MZ twins numerically exceeded DZ correlations, there was no substantial difference between the two groups. This result suggests that common environmental influences gained strength relative to genetic effects in determining BRS phenotype. However the ACE models could not reinforce this finding – supposedly due to the small sample size.

Similarity between twin siblings originates from additive genetic and common environmental influences. Related to BRS results in table 4, it can be seen, that despite the difference between average A and C values, the confidence intervals of the two variance components are significantly overlapping.

Based on these results we can conclude, that arterial baroreflex-function is determined mainly by environmental effects while genetic effects possess a minor role driving the variability of BRS phenotype.

Our data indicates that MZ correlations related to CCA stiffness parameters are exceeding DZ intra-twin correlations by more then a factor of 2. This pattern suggests that variance of the stiffness phenotype are dominated by additive and epistatic genetic effects. The ACE models further reinforced these findings. Table 4 results indicate, that arterial elasticity and stiffness were determined by additive genetic influences (~60%), while the remaining 40% of variability was driven by unique environmental effects.

Based on these results we can conclude, that CCA elasticity/stiffness shows a moderately strong inheritance, while the environment exerts a minor influence on this phenotype.

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