

Autonomic function in congenital heart defects

PhD-thesis

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Introduction

Congenital heart disease with septal defects

Congenital heart defects are the most common type of birth defects, 30% of the congenital diseases are heart defects. Eight children out of thousand live-births are born with congenital vitium.

The heart development begins in the third week of the pregnancy. Neural crest cells migrate to the area of the heart tube and play a pivotal role in initiating cardiac septation. Surgical ablation of these neural crest cells results in various forms of congenital heart diseases with septal defects such as Tetralogy of Fallot (ToF) and transposition of the great arteries (TGA).

Tetralogy of Fallot is the most common cyanotic congenital vitium. The complex heart defect involves four cardiovascular abnormalities: ventricular septal defect, pulmonary stenosis, overriding aorta and postnatal developing right ventricular hypertrophy. Usually the cyanotic symptoms and the characteristic hypoxic spells appear in six months after birth. The treatment is primarily surgical. After various palliative operations and total surgical repairs the short- and long-term survival of patients with Tetralogy of Fallot is good, however, arrhythmias often occur in the adulthood. The arrhythmias may lead to sudden cardiac death. ToF patients have hundred times greater risk for sudden cardiac death than the healthy population.

Transposition of the great arteries gives approximately 5% of the congenital heart defects. The congenital vitium involves abnormal spatial arrangement of the great vessels which results in separated systemic and pulmonary circulation: the aorta originates from the right ventricle while the pulmonary artery rises from the left chamber. The cyanosis appears already in the neonatal period or in the early infancy which makes the surgical intervention urgent. With the semi palliative Senning- (or atrial switch) procedure a baffle is created within the atria and reroutes the deoxygenated blood coming from the venae cavae towards the mitral valve. After the Senning surgical repair an increased, late,

arrhythmia-related mortality has been observed. Patients with TGA have a threefold risk for sudden cardiac death when compared with ToF patients. The underlying mechanism that leads to arrhythmias in ToF and TGA patients is not clear.

Sympathovagal balance and risk for arrhythmias

The sinuatrial node and the electrical cardiac conduction system of the heart are richly innervated by both limbs of the autonomic nervous system. If the activity of parasympathetic fibres that innervate the heart (cardiovagal fibres) increases, it will reduce the heart rate and conduction velocity whereas the sympathetic influence enhances these. The resting cardiovagal activity is a major determinant of the cardiovascular health. Healthy, middle-aged subjects with reduced cardiovagal activity and higher heart rates (>75 beat/min) have an almost four times greater risk for sudden cardiac death than healthy subjects with lower heart rates.

In healthy subjects the heart rate is not constant, but it fluctuates around a given value primarily due to changes in vagal activity. The analysis of heart rate variability (HRV) gives therefore estimates for the cardiac parasympathetic activity. Reduced HRV indicates deteriorated parasympathetic and simultaneously increased sympathetic activity. The shift in sympathovagal balance toward the sympathetic limb results in increased risk for arrhythmias. After myocardial infarction, for instance, reduced HRV was found to be an independent risk factor.

A major determinant of the cardiovagal activity is the arterial baroreflex. The baroreflex plays an important role in the short-term blood pressure regulation. An elevation in blood pressure distends the aortic arch and the carotid sinus and increases the strain of the vessel wall. Stretch-sensitive baroreceptors are located in these vascular segments, their firing frequency increases with rising pressures. The baroreflex mediates reductions in heart rate and total peripheral resistance, the blood pressure decreases and the negative feedback loop is complete. The cardiovagal baroreflex-sensitivity (BRS) can be quantified by the

coupling between appropriate changes in blood pressure and RR-intervals (RRI). There are two widely accepted methods for quantifying BRS: the spontaneous and the pharmacological technique. Indices of the cardiovascular baroreflex-sensitivity were found to be reduced in many diseased states; reduced BRS parameters were proved to be independent risk factors for arrhythmias after myocardial infarction, similarly to reduced HRV indices.

Patients with Tetralogy of Fallot were found to display reduced HRV and BRS indices. Furthermore, BRS indices were also found to be predictors of cardiovascular mortality in these patients. Autonomic function has never been investigated in patients with TGA.

Distensibility of the baroreceptor vessel wall and the baroreflex

Large elastic vasculature has a great significance in maintaining physiological hemodynamics, reduced elasticity of the elastic arteries was found to be an independent cardiovascular risk factor. Beyond the hemodynamic significance the elastic properties of the great vessels determine the baroreflex-sensitivity substantially. The change in blood pressure is followed by an alteration of the vascular diameter; consequently the adequate stimulus for the baroreceptors embedded in the aortic arch and the carotid sinus depends on the distensibility of the baroreceptor vessel walls. We have found that the distensibility of the carotid artery is responsible for 60% of variability observed in the baroreflex-sensitivity. The BRS can be divided into two components: the mechanical and the neural component. The distensibility of the baroreceptor vessel walls gives an estimate for the mechanical BRS. Since a tight correlation has been described between the distensibility of the aortic arch, carotid sinus and the common carotid artery, the mechanical BRS can be often characterized by the distensibility of the common carotid artery.

We have shown earlier that the mechanical component of the BRS, alias the distensibility of the common carotid artery declines gradually with advancing age, while the neural component increases till the end of adolescence. In certain diseased states such as

atherosclerosis and coronary artery disease, the mechanical BRS is reduced. In other pathological conditions such as Parkinson's disease or diabetic neuropathy, the neural component of the BRS is deteriorated.

Reduced elasticity of the aorta has been found in ToF, the impairment of the elastic function was proximally the most severe. We have found earlier that carotid artery elasticity is reduced in TGA patients compared with healthy controls.

Aims

We aimed to find answers to the following questions:

1. Is the carotid artery elastic function impaired in patients with Tetralogy of Fallot compared with healthy controls?
2. Is the (reduced) distensibility of the carotid artery related to reduced baroreflex-sensitivity in ToF patients?
3. Is baroreflex-sensitivity and heart rate variability reduced in patients with transposition of the great arteries after atrial switch operation compared with healthy controls?
4. Is the impaired carotid artery elastic function related to baroreflex-sensitivity in TGA patients?

Subjects and methods

Subjects

45 ToF-patients (27 men, 18 women, aged 6-56) and 32 TGA-patients who underwent Senning-procedure (23 boys, 9 girls, aged 9-19) were enrolled from the Gottsegen György Cardiology Institute, Budapest, Hungary. All patients were in clinical status I according to the functional classification of the New York Heart Association (NYHA). The patients did not take regular medication. The patients or their parents gave written informed consent to take part in the study which was approved by the Ethical Committee of the Semmelweis University, Hungary (207/2003). The results of our patients were compared with data of age- and gender-matched healthy control subjects.

Measured parameters

Blood pressure: In order to determine baroreflex-sensitivity radial artery beat-to-beat blood pressure was recorded continuously with applanation tonometry (Colin CBM-7000 AB-Instruments, Hastings, UK). To calculate carotid artery elastic variables, carotid artery blood pressure was obtained by applanation tonometry (SPT-301, Miller Instruments, Houston, Texas, USA), as well. Radial and carotid artery blood pressure curves were calibrated with brachial artery diastolic and mean blood pressure values measured by sphygmomanometry.

Carotid artery ultrasonography: To calculate common carotid elasticity, carotid artery diameter, pulsatile distension and intima-media thickness (IMT) was determined by high-precision ultrasonography. The ultrasound system consists of two parts, a regular ultrasound scanner (Scanner 200 Pie Medical, Maastricht, The Netherlands) and a vessel wall echotracking system (Wall Track system, WTS, Pie Medical, Maastricht, The Netherlands). WTS detects and follows the changes in the vessel diameter during the cardiac cycle. The left carotid artery was scanned by a 7.5 MHz transducer in 2D-mode and the movement of the anterior and posterior walls of the carotid artery was followed in a selected vascular section in M-mode.

ECG and respiration: ECG was recorded in standard Einthoven lead II. The respiratory frequency of our patients was standardized by a metronome (0.25 Hz).

Calculated parameters

Elastic variables of the carotid artery: Based on the registered end-diastolic diameter (D), pulsatile distension (ΔD), and carotid artery systolic (SBPc), diastolic (DBPc) and pulse pressure (PPc) the following carotid artery elastic variables were determined: distensibility coefficient (DC)= $(2 \times \Delta D \times D + \Delta D^2) / (PPc \times D^2)$ and incremental elastic modulus (Einc)= $[3 \times (1 + LCSA / IMCSA)] / DC$, where $LCSA = \pi (D^2) / 4$ carotid artery lumen cross-sectional area, $IMCSA = \pi (D / 2 + IMT)^2 - \pi (D / 2)^2$ intima-media cross-sectional area. The higher is the distensibility coefficient and the smaller is the incremental elastic modulus the more elastic is the vascular segment.

Baroreflex-sensitivity: BRS was calculated with the WinCPRS program (Absolute Aliens Oy, Turku, Finland). The program analyzed the relation between the blood pressure and the RR-intervals.

- During the pharmacological method bolus injection of alpha-1 agonist phenylephrine ($3\text{-}5\mu\text{g}\times\text{kg}^{-1}$) was given intravenously. The drug caused a 20-30 mmHg elevation in the systolic blood pressure, which caused reduction in the heart rate via baroreflex. RRIs were plotted against appropriate SBP values, and the slope of the regression line was defined as BRS. The measurement was accepted only if the correlation coefficient of the regression line was above 0.8. The BRS_{phe} was calculated as the average of three BRS values of successful measurements.
- The spontaneous method is based on the coupling between spontaneous fluctuations in systolic blood pressure and heart rate. The WinCPRS computed the time series of the systolic blood pressure and RRIs and identified the sequences in which systolic blood pressure and RRI-s concurrently increased over more than three consecutive beats. The minimal accepted change was 1

mmHg for systolic blood pressure and 5 ms for RRI. BRS_{sp} was the slope of the regression line fitted on the systolic blood pressure-RRI plot. Only sequences with a correlation coefficient > 0.85 were considered.

Heart rate variability: From 10 minute long RRI recording the WinCPRS program determined the time domain HRV-index, RMSSD (the root mean square of the successive RRI-difference), and the frequency domain index, HF (power spectral density of the RRI-variability in the high frequency range (0.15-0.4 Hz)).

Statistical analysis

Relationships between variables within each group were analyzed by Pearson's correlation test. Multiple regression analysis was performed to select the independent determinants of the autonomic indices in patients. Differences in variables between patients and controls were analyzed by unpaired t-tests or Mann-Whitney rank-sum for data failing tests of normality. Significance was accepted at $p < 0.05$.

Protocol

Subjects were studied in the early afternoon under standardized conditions. After a 10-15 minute long resting period in supine position the carotid measurements started. Carotid artery pressure on the right side, and diameter on the left side were recorded in 5-7 epochs, each epoch contained 4-6 distension waves. RRI and radial artery pressure were recorded for 10 minutes continuously with paced breathing to determine HRV- and BRS-indices. Finally, BRS_{phe} was also determined in selected group of patients and controls. The bolus injections of phenylephrine were repeated 3-4 times with approximately 10-15 minutes between each until baseline conditions were re-established.

Results

Distensibility of the carotid artery in ToF patients

There was no detectable anthropometric difference between patient and control groups. The brachial and carotid artery diastolic pressures were significantly lower, therefore pulse pressures were significantly higher and mean pressures were lower. Despite the larger central pulse pressure carotid artery pulsatile distension was markedly smaller in ToF patients. Carotid artery DC was reduced and Einc was increased in patients compared with controls, indicating the deterioration of the carotid artery elastic function. Carotid artery IMT was increased in patients when compared with controls. The carotid artery elastic variables did not show correlation with IMT in patients. When we compared ToF patients with healthy controls matched in pulse pressure, the carotid elastic parameters still indicated stiffening of the carotid artery. In ToF patients DC showed inverse correlation with age and carotid systolic blood pressure, both parameters were independent determinants of DC. Einc was related to age and carotid systolic pressure positively, only age was an independent determinant of the Einc.

Autonomic function and carotid artery distensibility in ToF

HRV and BRS indices were reduced in ToF patients than in healthy controls. The autonomic indices were inversely related to age, heart rate, systolic blood pressure and the carotid artery stiffness parameter, the incremental elastic modulus. The distensibility coefficient showed direct correlation with autonomic indices. Both BRS_{phe} and BRS_{sp} were positively and strongly related to distensibility coefficient. Multiple regression analysis indicated that distensibility coefficient was an independent determinant of BRS-indices.

Transposition of the great arteries

TGA patients weighted significantly less than healthy controls. The brachial artery systolic blood pressure was increased, the diastolic blood pressure was decreased, resulting in elevated pulse pressure. Carotid artery pulse pressure was also significantly higher in ToF patients which indicate stiffening of the large arteries. The pulsatile distension was reduced in patients and the carotid artery elastic parameters also indicated significant vascular stiffening. Carotid artery elastic variables did not show correlation with age. BRS_{sp} - and HRV-indices did not differ between ToF patients and control subjects. ToF patients exhibited a tendency towards having reduced BRS_{phe} -indices, but the difference did not reach statistical significance. We have found strong direct relationship between DC and BRS_{phe} , however, there was no such correlation in TGA patients.

Conclusions

Carotid artery elasticity is reduced in ToF patients

Stiffening of the large elastic arteries appears to affect both proximal and more distal vascular segments such as the carotid artery. Experimental data may provide a biological explanation for these findings. The neural crest cells first induce the ventricular and aorticopulmonary septation then they migrate towards the periphery and generate the elastic lamellae of the large arteries. This developmental hypothesis is supported by histological data: fragmented elastic lamellae and increased collagen/elastin ratio has been described in human aortic biopsy specimens obtained from patients with congenital heart defects. Increased IMT may also indicate abnormal vascular development. Since we have found no relation between IMT and carotid artery elastic parameters in ToF patients, it can be hypothesized, that thickening of the vascular wall and impairment of the elastic function originate in different histopathological reasons.

It is well established that arterial stiffness is an independent risk factor for cardiovascular morbidity. The significance of the increased carotid artery stiffness is not yet clear in ToF patients and further investigations are necessary to elucidate that, our findings may indicate an increased attendance for healthy lifestyle in ToF patients. Dietary modifications such as sodium restriction or omega-3 fatty acid rich diet may reverse carotid artery stiffening in ToF patients. Most of the ToF patients do not participate at P. E. classes, however, a moderate but regular physical activity would be advisable for those who lack adverse hemodynamic responses to exercise. Refraining from active and passive smoking may also affect large artery stiffness favorably.

Reduced distensibility of the central arteries results in impaired windkessel function. Due to this hemodynamic abnormality the left ventricular afterload will be increased and the coronary blood flow will be decreased. Beyond the hemodynamic problem the reduced carotid artery distensibility may influence the baroreflex function adversely.

Impaired carotid artery elastic function and reduced baroreflex-sensitivity are related in ToF patients

Since carotid artery elastic variables were independent determinants of BRS-indices, it can be concluded that the mechanism underlying reduced BRS is partially reduced distensibility of the carotid artery. Autonomic dysregulation in ToF patients can be explained by various intracardiac factors such as developmental abnormalities of the autonomic nerve fibers, surgical procedures and myocardial ischemia. Based on our findings, an extracardiac factor, namely reduced elasticity of the central arteries contributes to the impairment of autonomic functions. Impaired elastic function of the central arteries also damages the left ventricular function which was found to be an independent risk factor in ToF patients. Considering that BRS_{phe} is a prognostic factor in ToF patients, determination of baroreflex-sensitivity is paramount in these patients. However, because of its invasiveness, its determination faces severe problems. Based on our results, we plan the long-term follow up of our patient to determine the prognostic value of carotid artery distensibility. Measuring carotid DC is much easier and more available, therefore it could provide a valuable substitute for identifying ToF patients with high-risk for arrhythmias. We speculate that reversal of carotid artery stiffening by dietary modifications and regular physical activity would have an indirect favorable effect on baroreflex-sensitivity in ToF patients.

Despite reduced carotid artery distensibility autonomic function is preserved in TGA patients

Our present data indicate a complete recovery or reinnervation of the sinoatrial node late after repair in TGA patients. This hypothesis is supported by the finding that cardiac autonomic nerve fibers exhibited partial regeneration after reconstructive, arterial repair in TGA patients. Cardiac sympathetic and parasympathetic reinnervation was described after heart transplantation, as well. The mechanical component of BRS, the carotid artery distensibility is not the only determinant of the baroreflex function. Our results emphasize

the importance of the neural baroreflex-sensitivity. It is known that physical activity improves baroreflex function. According to recent publications mainly the neural component of the baroreflex increases not the carotid artery distensibility. Neural plasticity of the central baroreflex structures might explain these observations. As an effect of physical exercise the neuronal relationships go through transformation, new synapses are formed and the existing synapses become more active. In case of TGA patients we hypothesize that the reduction in baroreceptor input due to congenital vascular stiffening might be compensated by central autonomic adaptation maintaining BRS at levels close to normal. In contrast with TGA, HRV and BRS indices were found to be reduced in ToF patients. Our ToF patients were exposed to hypoxic conditions for a longer time period than TGA patients. We assume that low oxygen saturation levels compromised the neuronal capability for adaptation.

References

Publications closely related to the thesis

1. Pinter A, Laszlo A, Mersich B, Kadar K, Kollai M. (2007) Adaptation of baroreflex function to increased carotid artery stiffening in patients with transposition of great arteries. *Clin Sci (Lond)*. 113(1): 41-6.
2. Laszlo A, Pinter A, Horvath T, Kadar K, Temesvari A, Kollai M, Studinger P. (2011) Impaired carotid artery elastic function in patients with tetralogy of Fallot. *Heart Vessels*. 26(5): 542-8.

Other publications

3. Laszlo A, Pinter A, Horvath T, Kadar K, Kollai M, Studinger P. (2009) Az artéria carotis rugalmassága csökkent Fallot-tetralógiás gyermekekben. *Cardiologia Hungarica* 39(3): 212-216.
4. Horvath T, Pinter A, Kollai M. (2012) Carotid artery stiffness is not related to endothelial function in young healthy subjects. *Auton Neurosci*. 166(1-2): 85-8.
5. Pinter A, Horvath T, Sarkozi A, Kollai M. (2012) Relationship between heart rate variability and endothelial function in healthy subjects. *Auton Neurosci*. 169(2): 107-12.
6. Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S, on behalf of the Reference Values for Arterial Measurements C. (2012) Reference intervals for common carotid intima-media thickness measured with echotracking: relation with risk factors. *Eur Heart J*.
7. Pinter A, Horváth T, Kádár K, Kollai M. (2012) Nagyér-transzpozícióban az arteria carotis csökkent rugalmassága nem rotja a cardiovascularis autonóm funkciót. *Orvosképzés_1*:29-34.