Adaptation of baroreflex function to increased carotid artery stiffening in patients with transposition of great arteries

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ABSTRACT

We have shown previously that TGA (transposition of great arteries) is associated with increased carotid artery stiffness. It has been established that stiffening of the barosensory vessel wall results in reduced baroreceptor activation and impaired BRS (baroreflex sensitivity). In the present study we tested the hypothesis that the increased carotid artery stiffness in TGA patients was associated with reduced cardiovagal BRS. We studied 32 TGA patients aged 9–19 years, 12 ± 3 years after surgical repair and 32 age-matched healthy control subjects. Carotid artery diastolic diameter and pulsatile distension was determined by echo wall tracking; carotid blood pressure was measured by tonometry. BRS was measured using spontaneous techniques [BRSseq and LFgain (low-frequency transfer function gain)] and by the phenylephrine method (BRSphe). Carotid artery distensibility was markedly reduced in patients as compared with controls (5.6 ± 1.9 × 10^-3 compared with 8.7 ± 2.7 × 10^-3/mmHg P < 0.05, as determined using an unpaired Student’s t test), but BRS was not different in patients and controls (20.3 ± 14.7 compared with 21.7 ± 12.7 for BRSseq; 13.1 ± 9.2 compared with 10.6 ± 4.5 for LFgain; and 19.1 ± 8.6 compared with 24.8 ± 7.2 for BRSphe respectively). Carotid artery elastic function was markedly impaired in patients with TGA, but the increased stiffness of the barosensory vessel wall was not associated with reduced BRS. It appears that attenuation of baroreceptor stimulus due to arterial stiffening may be compensated by other, possibly neural, mechanisms when it exists as a congenital abnormality.

INTRODUCTION

TGA (transposition of great arteries) is a congenital heart defect in which the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. TGA is the consequence of abnormal aortico-pulmonary septal development. Although after surgical correction these TGA patients have a good long-term prognosis, they also have considerable late morbidity and mortality caused, in part, by rhythmic disturbances [1–3]. The mechanism of these rhythmic disturbances is not clear.

In animal models, experimentally induced defects in aortico-pulmonary septation was found to be associated with impaired large artery elastogenesis [4,5]. In line with this observation we have recently demonstrated that the carotid artery was markedly stiffer in TGA patients than in age-matched controls [6]. Stiffening of large elastic arteries, in which high-pressure baroreceptors are

Key words: baroreceptor, baroreflex function, carotid artery stiffness, congenital abnormality, transposition of great arteries (TGA).

Abbreviations: ASD, atrial septal defects; BMI, body mass index; BRS, baroreflex sensitivity; BRSphe, BRS determined using the phenylephrine method; DBP, diastolic blood pressure; HRV, heart rate variability; LF, low frequency; LFgain, LF transfer function gain; RRI, RR interval; RVOTR, right ventricular outflow tract reconstruction; SBP, systolic blood pressure; TGA, transposition of great arteries; ToF, tetralogy of Fallot; VSD, ventricular septal defects.

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embedded, has been shown to be associated with reduced cardiovagal BRS (baroreflex sensitivity) [7–13]. Impaired baroreflex function shifts cardiac autonomic balance towards sympathetic dominance, promoting the occurrence of arrhythmic events [14]. Reduced BRS has been established as an independent predictor of mortality in heart failure and after myocardial infarction [15,16]. Baroreflex function has never been studied in congenital heart disease, including TGA.

In the present study, we tested the hypothesis that increased carotid artery stiffness in TGA patients was associated with reduced BRS and altered cardiovagal autonomic function in the postoperative state.

MATERIALS AND METHODS

Subjects
Thirty-two TGA patients (23 male and nine female) aged 9–19 years were recruited from the Gottsegen Cardiology Institute, Budapest. Patients had an atrial switch operation (Senning procedure), which was performed between the ages of 6 months and 3 years; the average time after repair was 12 ± 3 years. The Senning procedure creates a tunnel between the atria, redirecting oxygen-rich blood to the right ventricle and aorta and the oxygen-poor blood to the left ventricle and pulmonary artery. Exclusion criteria included permanent pacing, atrial fibrillation or > two ectopic beats/min during data acquisition, clinical instability within the preceding 2 months, hypertension and diabetes mellitus. Surgical data were obtained from operative notes. All patients were in clinical status Class I as defined according the New York Heart Association functional classifications, and none of the children were taking any medication. Thirty-two age-matched healthy control subjects were also studied. All subjects gave written informed consent to participate in the study, which was approved by the Ethical Committee of the Semmelweis University, Budapest, Hungary.

Blood pressure
Radial artery pressure was monitored continuously with an automated tonometric device (Colin CBM-7000; AD Instruments) for determination of BRS indices. During data collection the servo-reset mechanism of the Colin apparatus was turned off to permit continuous data acquisition. SBP and DBP (systolic and diastolic blood pressure respectively) values, measured on the brachial artery by an automatic microphonic sphygmomanometer built into the Colin device, were used to calibrate the radial pressure pulse.

ECG and respiration
ECG was recorded continuously from the limb lead with the largest R wave. Respiration was recorded with an inductive system (Respitrace System; Ambulatory Monitoring).

Carotid ultrasonography
The diameter of the left common carotid artery and its pulsatile distension were measured by ultrasonography, with the scanner was positioned 1.5 cm proximal to bifurcation. The ultrasound device consisted of a vessel wall echo-tracking system (Wall Track System; Pie Medical) and has been described in detail previously [17]. The carotid artery diameter was recorded in five epochs, each containing 4–8 distension pulses.

Carotid artery pressure
Carotid artery pressure was measured by applanation tonometry (SPT-301; Millar Instruments), and the carotid pulse wave recording was calibrated using diastolic and mean brachial pressure values measured by sphygmomanometry on the right brachial artery. Diastolic brachial pressure was assigned to the minimum value of the carotid pressure pulse wave and the mean pressure to its electrically averaged value [18]. The carotid tonometric pressure was used to calculate carotid artery elastic parameters.

Carotid artery elastic variables
The distensibility coefficient was calculated as $2 \times \Delta D(D \times \Delta P)$, where $D$ is the end-diastolic diameter, $\Delta D$ is the change in diameter from end-diastole to peak systole and $\Delta P$ is carotid pulse pressure. The stiffness index was expressed as $\ln (SP/DP) \times D/\Delta D$, where $SP$ and $DP$ are systolic and diastolic carotid pressures respectively.

BRS

Spontaneous methods
The coupling between spontaneous fluctuations in heart rate and systolic pressure was determined using the sequence method and also by spectral analysis. The software used (WinCPRS program; Absolute Aliens Oy) detected the ECG R wave and computed RRI (RR interval) and radial artery SBP time series and identified spontaneously occurring sequences in which SBP and RRI concurrently increased and decreased over three or more consecutive beats (BRSseq). The minimal accepted change was 1 mmHg for SBP and 5 ms for RRI. Only sequences with a correlation coefficient >0.85 were considered. To determine spectral indices, the signals were interpolated, resampled and their power spectra were determined using FFT-based methods. The $LF_{gain}$ [$LF$ (low-frequency) transfer function gain] was determined, which expresses RRI and SBP cross-spectral magnitude in the frequency range of 0.05–0.15 Hz, where coherence is greater than 0.5.

Phenylephrine method
In 18 of our patients and in 18 control subjects bolus phenylephrine injections (3–4 µg kg$^{-1}$) were given intravenously, which caused a 10–25 mmHg elevation in
SBP. Injections were repeated 3–4 times with approximately 5–10 min between each, until baseline conditions were re-established. RRIs were plotted against SBP values, and the slope of the regression line was determined as BRSphe. Only regression lines that were statistically significant ($P < 0.05$) were accepted for analysis. The final slope was obtained by calculating the mean value of $\geq$ two measurements.

**HRV (heart rate variability)**

Time and frequency domain measurements of HRV from 10 min recordings of RRIs were calculated using the WinCPRS program. The following parameters were determined: the S.D. of the RRI (termed NNSD), the root-mean-square of successive differences (termed RMSSD), the percentage of successive RRIs which differed by more than 50 ms (termed pNN50) and LF (0.05–0.15 Hz) and high-frequency (0.15–0.4 Hz) power of RRI variability.

**Protocol**

Subjects were studied in the early afternoon under standardized conditions, in a quiet room at a comfortable temperature. All fasted at least 2 h before testing and were asked to refrain from strenuous exercise or drinking alcohol or caffeine-containing beverages for 24 h prior to the study. Upon arrival at the investigation unit the subjects were equipped with measurement devices, and then rested in the supine position for approx. 15 min until the absence of evident heart rate and mean blood pressure trends demonstrated that satisfactory baseline conditions had been achieved. The protocol began with the carotid measurements. Carotid artery tonometric pressure on the right side, and diameter on the left side were recorded simultaneously in 5–7 epochs, each containing 4–8 distension pulses; the recordings were used to determine carotid elastic parameters. Patients were then asked to synchronize their respiratory rate with a metronome beating at 0.25 Hz. RRI and radial artery pressure were recorded continuously for a 10 min period to determine spontaneous baroreflex indices, and then BRSphe (BRS determined using the phenylephrine method) was also measured in selected patients.

**Data analysis**

Blood pressure and ECG recordings of 10 min duration were digitized and analyzed using the WinCPRS program using a sampling rate of 500 Hz and stored in a personal computer for subsequent off-line analysis. Data were expressed as means ± S.D. Differences in variables between controls and patients were analyzed using unpaired Student’s $t$ tests or Mann–Whitney rank-sum for data failing tests of normality. Relationships between variables were investigated by univariate correlation analyses. Significance was accepted at $P < 0.05$. Statistical analysis was performed using the SigmaStat for Windows Version 2.03 (SPSS) program package.

**RESULTS**

Clinical characteristics and carotid artery variables of patients and controls are given in Table 1. Patients had a lower BMI (body mass index) compared with controls. SBP was higher and DBP was lower in patients compared with controls, resulting in a higher pulse pressure amplitude but no change in mean arterial pressure. The carotid artery end-diastolic diameter was smaller and pulsatile distension was less in patients in spite of higher carotid pulse pressure. Elastic parameters indicated significant stiffening of the carotid artery, in support of our earlier observations. Carotid distensibility was decreased with age in controls ($r^2 = 0.45$, $P < 0.05$), whereas it was not related to age in TGA patients. Carotid distensibility was inversely related to SBP in both patients and controls ($r^2 = 0.35$, and $r^2 = 0.31$ respectively, $P < 0.05$ for both).

Table 1  Clinical characteristics, carotid artery dimensions and elastic variables of TGA patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
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<tr>
<td>Age (years)</td>
<td>12.2 ± 3.0</td>
<td>13.1 ± 2.8</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>18.1 ± 3.0*</td>
<td>20.4 ± 1.6</td>
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<tr>
<td>SBP (mmHg)</td>
<td>115 ± 10*</td>
<td>105 ± 12</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>62 ± 7*</td>
<td>66 ± 9</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>79 ± 7</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75 ± 12</td>
<td>78 ± 11</td>
</tr>
<tr>
<td>ΔP (mmHg)</td>
<td>47 ± 11*</td>
<td>36 ± 10</td>
</tr>
<tr>
<td>D (µm)</td>
<td>5647 ± 425*</td>
<td>5993 ± 510</td>
</tr>
<tr>
<td>ΔD (µm)</td>
<td>698 ± 142*</td>
<td>876 ± 163</td>
</tr>
<tr>
<td>DC (10⁻³/mmHg)</td>
<td>5.6 ± 1.9*</td>
<td>8.7 ± 2.7</td>
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<td>Stiffness index</td>
<td>4.7 ± 1.6*</td>
<td>3.2 ± 1.0</td>
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Table 2  HRV and spontaneous BRS indices of TGA patients and control subjects

Values are means ± S.D. NNSD, S.D. of RRI; RMSSD, root-mean-square of successive RRI differences; pNN50, percentage of RRI which differ more than 50 ms; HF, high-frequency (0.15–0.4 Hz) power of RRI variability; LF, low-frequency (0.05–0.15 Hz) power of RRI variability; BRSseq, baroreflex sensitivity determined using the sequence method. No significant differences were found at P < 0.05, when groups were compared for differences using Student's t tests or the Mann–Whitney rank-sum for data failing tests of normality.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td>NNSD (ms)</td>
<td>77.3 ± 39.6</td>
<td>66.6 ± 25.0</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>76.2 ± 55.7</td>
<td>61.5 ± 37.7</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>28.7 ± 21.3</td>
<td>27.3 ± 21.4</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>2027 ± 2620</td>
<td>1625 ± 2139</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>1733 ± 1560</td>
<td>1029 ± 679</td>
</tr>
<tr>
<td>BRSseq</td>
<td>20.3 ± 14.7</td>
<td>21.7 ± 12.7</td>
</tr>
<tr>
<td>LFgain</td>
<td>13.1 ± 9.2</td>
<td>10.6 ± 4.5</td>
</tr>
</tbody>
</table>

Figure 1  BRS determined by phenylephrine (BRSphc) is directly related to carotid distensibility in controls (○, r = 0.71, P < 0.05) but no relationship exists in TGA patients (△).

In the control subjects, BRSphc was significantly and directly related to carotid artery distensibility (r² = 0.53, P < 0.05), as expected, whereas no such relationship existed in patients. When patients’ data were inserted into the control BRSphc-carotid distensibility nomogram, ten patients had higher BRSphc values than the upper 95% confidence limits of control data (Figure 1). Spontaneous BRS and HRV indices were not related to age or systolic pressure in either patients or controls.

DISCUSSION

In the present study we compared carotid artery elasticity and BRS indices in TGA patients after surgical correction with age-matched healthy control subjects, and found that: (i) elastic variables indicated significant stiffening of the carotid artery in patients confirming earlier results; (ii) reduced distensibility of the carotid artery was not associated with reduced BRS; and (iii) cardiovagal autonomic indices were not significantly different between patients and controls.

BRS and HRV

BRS and HRV have been established as independent predictors of cardiovascular morbidity and mortality. There are only a handful of studies, however, in which these indices have been determined in congenital heart disease. Some of these studies indicated reduced BRS and HRV in various forms of congenital heart disease, both before and after surgical intervention [19–24]. In patients late after the Fontan operation and also in patients after repair of ToF (tetralogy of Fallot), autonomic nervous control of the heart was found to be markedly deranged, with reduced BRS and HRV [19–22]. The reduction was related to previous surgical interventions, their timing and underlying right- and left-sided haemodynamics [22]. In another study on ToF patients, however, only 43% of patients had lower HRV values [21]. In a study on patients with ASD (atrial septal defects) or VSD (ventricular septal defects), or with RVOTR (right ventricular outflow tract reconstruction), BRS and HRV were lower than controls, with the reduction, however, being less in ASD and VSD than in RVOTR. The reduction in BRS and HRV was greater immediately after surgery, but partially recovered later on. HRV and BRS inversely correlated with the number of surgical procedures and directly correlated with the follow-up duration after RVOTR [23]. BRS and HRV, however, has never been studied in patients with TGA.

The results of the present study indicate no significant differences in cardiovagal autonomic indices between TGA patients and control subjects. This finding was unexpected, considering the unavoidable damage to cardiac autonomic nerves during surgery. Cardiopulmonary nerves, which pass along the posteroomedial surface of the superior vena cava and the right atrium, formplexuses which contain both vagal and sympathetic cardiac efferent fibres, together with afferents of cardio-pulmonary origin. Consequently, removal of pericardium overlying the right atrium during correction surgery of TGA must cause mechanical damage to cardiac autonomic innervation. Additional damage may also occur due to ischaemia of nerves and/or of sinoatrial node. Indeed in two studies, when autonomic indices were compared before and immediately after corrective surgery, the postoperative values were markedly reduced [23,24]. Therefore our present data may indicate complete recovery or re-innervation of the sinoatrial node late after repair in TGA patients. In the rat model, re-innervation in the baroreceptor region was observed a few months after
sino-aortic denervation [25]. The question arises as to what might explain the difference in the extent of autonomic recovery between the present study and earlier reports. Two factors may be considered. Firstly, the difference in time after repair. Autonomic indices were found to recover with time after corrective surgery; in the study by Ouchi et al. [23], BRS significantly correlated with the follow-up duration after RVOTR. However, the difference in time after repair seems an unlikely explanation in our present case, because HRV and BRS were found to be lower even 26 years after repair ofToF [22], whereas in the present study the mean \( \pm S.D. \) time after repair was only 12 \( \pm 3 \) years. Second, the difference in the complexity of surgery. In the complex forms of congenital heart disease, reduction in HRV and BRS was inversely related to the number of surgical procedures. In the atrial switch type of repair the corrective surgery of TGA is limited to the right atrium and does not involve the ventricular septum, the right ventricular outflow tract or the pulmonary artery. It seems possible that more extensive surgical damage to cardiac tissues and to areas where cardiopulmonary baroreceptors may be located can result in long-term impairment of baroreflex function.

Lack of relationship between carotid artery distensibility and BRS

Previous investigations have demonstrated that BRS is significantly related to carotid artery distensibility. A positive association between elastic properties of the carotid artery and BRS has been reported in healthy volunteers, pregnant women and hypertensive patients [7,8,11]. Age-associated changes in BRS were found to be related to central arterial compliance [10]. Regular exercise in sedentary older subjects increased both cardiovagal BRS and carotid artery compliance and the two events were strongly and positively related [12]. In healthy volunteers an approximately 50% variation in BRS was explained by differences in carotid artery distensibility [7,10,13]. It might be argued that the relatively low number of patients prevented the difference in BRSphe in patients compared with controls to reach statistical significance. On the other hand, the complete lack of a relationship between BRS and carotid artery distensibility in patients indicates that BRS is determined, at least in part, by different mechanisms in patients compared with controls.

Although the ability of barosensory vessels to transduce arterial pressure changes into vessel wall stretch is a key mechanism in baroreflex function, recent findings have emphasized an important role of neural function, which encompasses baroreceptor output, afferent neural conduction, central integration, efferent autonomic outflow and sinoatrial node responsiveness [13]. In one study carotid artery distensibility was found to decrease from early childhood, with a concomitant increase in BRS until puberty [26]. This finding indicated that, in spite of unremitting vascular stiffening, maturation of neural function predominantly determines baroreflex gain during this period of life [26]. In another study vascular and neural deficits were both shown to contribute to an age-related decline in cardiovagal BRS, whereas short-term exercise attenuated this decline primarily by maintaining neural vagal control [27]. These observations indicate that neural plasticity might play an important role in determining cardiovascular autonomic regulation. Neural plasticity might also explain the findings of the present study. 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.

Limitations

Due to the cross-sectional design of the present study, we could not examine the direct influence of surgical procedures on either arterial stiffness or cardiac autonomic control. Also, we were not able to establish whether the normal HRV and BRS values that we observed in our TGA patients were the result of gradual improvement after a postoperative decline, and whether carotid artery stiffening was the result of gradual postoperative derangement in vessel wall distensibility. The number of patients in whom BRSphe was performed was relatively low, because many of our patients were reluctant to undergo the phenylephrine procedure.

We measured carotid arterial diameter in the common carotid artery, \( \sim 1 \) cm below the carotid bulb housing the carotid sinus baroreceptors. It is difficult to measure the diameter of the carotid bulb because its shape is oval and the opposing walls are not parallel. Measurement of common carotid arterial compliance may not be identical with that of the adjacent carotid bulb or the aortic arch. Nonetheless, it is likely that this measurement is more representative of local vascular wall properties than measurements made from more peripheral vessels. We did not assess diameter and blood pressure changes in the aorta, which is also richly innervated with arterial baroreceptors. Because the stimulus to these two receptor regions is directionally similar during phenylephrine administration and both vessels demonstrate similar mechanical and haemodynamic properties, this should not represent a significant confound in the present study. However, we cannot exclude this possibility.

ACKNOWLEDGMENTS

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