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Alexandra Pinter, Beatrix Mersich, Andrea Laszlo, Krisztina Kadar, Mark Kollai. Adaptation of baroreflex function to increased carotid artery stiffening in patients with transposition of great arteries. *Clinical Science*, 2007, 113 (1), pp.41-46. 10.1042/CS20060363. hal-00479359

**HAL Id: hal-00479359**

**<https://hal.science/hal-00479359>**

Submitted on 30 Apr 2010

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

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Acknowledgements: This work was supported by the Hungarian National Research Fund, grant OTKA – T 049690 and the Ministry of Health, grant ETT-054/2006

We have shown before that transposition of great arteries (TGA) 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 baroreflex sensitivity. In this study we tested the hypothesis that the increased carotid artery stiffness in TGA patients was associated with reduced cardiovagal baroreflex sensitivity (BRS).

We studied 32 TGA-patients aged 9–19 yrs,  $12 \pm 3$  yrs after surgical repair and 32 healthy control subjects matched for age. Carotid artery diastolic diameter and pulsatile distension was determined by echo wall-tracking; carotid blood pressure was measured by tonometry. BRS was measured by spontaneous techniques ( $BRS_{seq}$ ,  $LF_{gain}$ ) and by the phenylephrine method ( $BRS_{phe}$ ). Carotid artery distensibility was markedly reduced in patients as compared with controls ( $5.6 \pm 1.9$  vs.  $8.7 \pm 2.7 \cdot 10^{-3}/\text{mmHg}$ ,  $p < 0.05$ , unpaired t-test), but baroreflex sensitivity was not different in patients and controls ( $20.3 \pm 14.7$  vs.  $21.7 \pm 12.7$  for  $BRS_{seq}$ ;  $13.1 \pm 9.2$  vs.  $10.6 \pm 4.5$  for  $LF_{gain}$ , and  $19.1 \pm 8.6$  vs.  $24.7 \pm 7.1$  for  $BRS_{phe}$  respectively).

Carotid artery elastic function is markedly impaired in patients with TGA, but the increased stiffness of the barosensory vessel wall is 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

Transposition of great arteries (TGA) 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 these TGA-patients after surgical correction have good long-term prognosis, they also have considerable late morbidity and mortality caused, in part, by rhythm disturbances (1, 2, 3). The mechanism of these rhythm 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 embedded, has been shown to be associated with reduced cardiovagal baroreflex sensitivity (7-13). Impaired baroreflex function shifts cardiac autonomic balance towards sympathetic dominance, promoting the occurrence of arrhythmic events (14). Reduced baroreflex sensitivity has been established as 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 this study, we tested the hypothesis that increased carotid artery stiffness in TGA patients was associated with reduced baroreflex sensitivity and altered cardiovagal autonomic function in the post-operational state.

## **MATERIALS AND METHODS**

### **Subjects**

Thirty-two TGA patients (23 male) aged 9 to 19 years were recruited from the Gottsegen Cardiology Institute, Budapest. Patients had an atrial switch operation (Senning-procedure), which was performed between the ages 6 months to 3 years; average time after repair was  $12 \pm 3$  years. The Senning-operation 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  $> 2$  ectopic beats per min during data acquisition, clinical instability within 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 was taking any medications. 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 Ltd., Hastings, UK) for determination of BRS indices. During data collection the servo-reset mechanism of the Colin apparatus was turned off to permit continuous data acquisition. Systolic and diastolic blood pressure values, measured on the brachial artery by an automatic microphonic sphygmomanometer built in 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 (Respirace System, Ambulatory Monitoring Inc.).

### **Carotid ultrasonography**

Diameter of the left common carotid artery and its pulsatile distension were measured with ultrasonography, 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, Maastricht, The Netherlands) and has been described in detail before(17). Carotid artery diameter was recorded in 5 epochs, each containing 4-8 distension pulses.

### **Carotid artery pressure**

Carotid artery pressure was measured by applanation tonometry (SPT-301, Millar Instruments, Houston, Texas, USA), and the carotid pulse wave recording was calibrated by 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 (DC) was calculated as  $2 \cdot \Delta D / (D \cdot \Delta P)$ , 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. Stiffness index was expressed as  $\ln(SP/DP) \times D / \Delta D$ , where SP and DP are systolic and diastolic carotid pressure, respectively.

### **Baroreflex-sensitivity (BRS)**

*Spontaneous methods:* The coupling between spontaneous fluctuations in heart rate and systolic pressure was determined by the sequence method and also by spectral analysis. The software (WinCPRS program, Absolute Aliens Oy, Finland) detected the ECG R-wave and computed RR-interval (RRI) and radial artery systolic blood pressure (SBP) time series and identified spontaneously occurring sequences in which SBP and RRI concurrently increased and decreased over three or more consecutive beats ( $BRS_{seq}$ ). 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 low-frequency transfer function gain ( $LF_{gain}$ ) was determined which expresses RRI and SBP cross-spectral magnitude in the frequency range of 0.05-0.15 Hz frequency band, where coherence is greater than 0.5.

*Phenylephrine-method:* In 18 of our patients and in 18 control subjects bolus phenylephrine injections (3-4  $\mu\text{g}/\text{kg}$ ) were given iv., which caused 10–25 mmHg elevation in systolic blood pressure. Injections were repeated 3–4 times with approximately 5–10 minutes between each, until baseline conditions were re-established. RR-intervals were plotted against systolic blood pressure values, and the slope of the regression line was determined as  $BRS_{phe}$ . 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  $\geq 2$  measurements.

### **Heart rate variability (HRV)**

Time and frequency domain measures of heart rate variability from 10 min recordings of RR-intervals were calculated using the WinCPRS program. The following parameters were

determined: the standard deviation of the RR-intervals (NNSD), the root mean square of successive differences (RMSSD), the percent successive of RR-intervals which differed more than 50 ms (pNN50) and low (0.05-0.15 Hz) and high frequency (0.15-0.4 Hz) power of RR-interval variability (LF and HF, respectively).

### **Protocol**

Subjects were studied in the early afternoon under standardized conditions, in a quiet room at a comfortable temperature. All fasted at least two hours before testing and were asked to refrain from strenuous exercise or drinking alcohol or caffeine containing beverages for 24 hours before the study. Upon arrival at the investigation unit the subjects were equipped with measurement devices, and then rested in supine position for about 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, which recordings were used to determine carotid elastic parameters. Then patients were asked to synchronize their respiratory rate with a metronome beating at 0.25 Hz. RR-interval and radial artery pressure were recorded continuously for a 10-min period to determine spontaneous baroreflex indices, then BRS was also determined by the phenylephrine-method in selected patients.

### **Data analysis**

Blood pressure- and ECG-recordings of 10 minutes duration were digitized and analyzed with the WinCPRS program using a sampling rate of 500 Hz and stored in a personal computer for subsequent off-line analysis. Data are expressed as mean  $\pm$  1SD. Differences in variables between controls and patients were analyzed by unpaired Student's t-test, or Mann-Whitney



rank-sum for data failing test of normality. Relations between variables were investigated by univariate correlation analyses. Significance was accepted at  $p < 0.05$ . Statistical analysis was performed by the SigmaStat for Windows Version 2.03 (SPSS Inc.) program package.

## RESULTS

Clinical characteristics and carotid artery variables of patients and controls are given in Table 1. Patients had lower BMI. Systolic pressure was higher in patients and diastolic pressure lower, resulting in higher pulse pressure amplitude but no change in mean arterial pressure. 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 decreasing 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 systolic blood pressure both in patients and controls ( $r^2 = 0.35$ , and  $r^2 = 0.31$ , respectively,  $p < 0.05$  for both).

Spontaneous BRS- and HRV-index values were not statistically different in patients and in controls (Table 2). Also, spontaneous BRS indices were not related to carotid artery elastic parameters neither across all subjects, nor within the patient and control groups. BRS was determined by the phenylephrine method ( $Phe_{brs}$ ) in 18 patients and in 18 control subjects. The obtained values for patients ( $19.1 \pm 8.6$  ms/mmHg) tended to be lower than those in controls ( $24.8 \pm 7.2$  ms/mmHg) but the difference did not reach statistical significance. In the control subjects  $Phe_{brs}$  was significantly and directly related to carotid artery distensibility ( $r^2 = 0.53$ ,  $p < 0.05$ ), as expected, whereas no such relationship existed in patients. When patients' data were inserted into the control  $Phe_{brs}$  – carotid distensibility nomogram, 10 patients had

higher  $Phe_{brs}$  values than the upper 95 % confidence limits of control data (Fig. 1). Spontaneous BRS and HRV indices were not related to age or systolic pressure neither in patients, nor in controls.

## **DISCUSSION**

We compared carotid artery elasticity and baroreflex sensitivity indices in TGA patients after surgical correction and in age matched healthy control subjects, and found, that: 1) elastic variables indicated significant stiffening of the carotid artery in patients confirming earlier results; 2) reduced distensibility of the carotid artery, was not associated with reduced baroreflex sensitivity; 3) cardiovagal autonomic indices were not significantly different in patients and controls.

### **Baroreflex sensitivity and heart rate variability**

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 were determined in congenital heart disease. Some of those results indicated reduced BRS and HRV in various forms of congenital heart disease, both before and after surgical interventions (19-24). In patients late after the Fontan operation and also in patients after repair of tetralogy of Fallot (ToF) 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 hemodynamics (22). In another study on ToF patients, however, only 43 % of patients had lower HRV values (21). In a study on patients with atrial (ASD) or ventricular septal defects (VSD), or with right ventricular

outflow tract reconstruction (RVOTR), BRS and HRV were lower than control, with the reduction, however, being less in ADS and VSD than in RVOTR. The reduction in BRS and HRV was greater immediately after surgery, but recovered partially later on. HRV and BRS correlated inversely with the number of surgical procedures and correlated directly with the follow up duration after RVOTR (23). BRS and HRV, however, has never been studied in patients with TGA.

Our present data 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 posteromedial surface of the superior vena cava and the right atrium, form plexuses, 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 ischemia 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). Our present data therefore, may indicate complete recovery or reinnervation 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 this study and earlier reports. Two factors may be considered: 1) *Difference in time after repair*. Autonomic indices were found to recover with time after corrective surgery; in the study of Ouchi et al. BRS significantly correlated with the follow-up duration after RVOTR [23]. Difference in time after repair, however, seems an unlikely explanation in our

case, because HRV and BRS were found to be lower even 26 years after repair of TOF [22], while in the present study the mean ( $\pm$  SD) time after repair was only  $12 \pm 3$  years. 2) *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 RVOT, or the pulmonary artery. It seems possible that the 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 relation between carotid artery distensibility and baroreflex sensitivity**

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 approximately 50% variance 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 baroreflex sensitivity determined by phenylephrine in patients vs. controls to reach statistical significance. On the other hand, the complete lack of relation between baroreflex sensitivity and carotid artery distensibility in patients indicate that baroreflex sensitivity is determined – at least in part – by different mechanisms in patients vs. controls.

Although the ability of barosensory vessels to transduce arterial pressure changes into vessel wall stretch is a key mechanism in baroreflex function, recent data emphasized the 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. This finding indicates 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 age related declines 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 explain our present findings, as well. We hypothesize that the reduction of baroreceptor input, due to congenital vascular stiffening, might be compensated by central autonomic adaptation, maintaining BRS at close to normal level.

### **Limitations**

Due to the cross-sectional design of the study, we could not examine direct influence of surgical procedures on either arterial stiffness or on 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 BRS was determined by the phenylephrine method is relatively low, because many of our patients were reluctant to undergo the phenylephrine procedure.

We measured carotid arterial diameter in the common carotid artery, ~ 1cm 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 to 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 BP changes in the aorta, which is also richly innervated with arterial baroreceptors. Because the stimulus to these 2 receptor regions is directionally similar during phenylephrine administration and both vessels demonstrate similar mechanical and hemodynamic properties, this should not represent a significant confound in the present study. We cannot exclude this possibility, however.

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	Patients	Controls
n(female)	32(9)	32(9)
age(yrs)	13.2 ± 3.0	13.1 ± 2.8
BMI[kg/m <sup>2</sup> ]	18.3 ± 3.0*	20.4 ± 1.6
SBP[mmHg]	115 ± 10*	105 ± 12
DBP[mmHg]	62 ± 7*	66 ± 9
MBP[mmHg]	79 ± 7	79 ± 9
HR[bts/min]	75 ± 12	78 ± 11
ΔP <sub>c</sub> [mmHg]	47 ± 11*	36 ± 10
D[μm]	5647 ± 425*	5993 ± 510
ΔD[μm]	698 ± 142*	876 ± 163
DC[10 <sup>-3</sup> /mmHg]	5.6 ± 1.9*	8.7 ± 2.7
stiffness index	4.7 ± 1.6*	3.2 ± 1.0

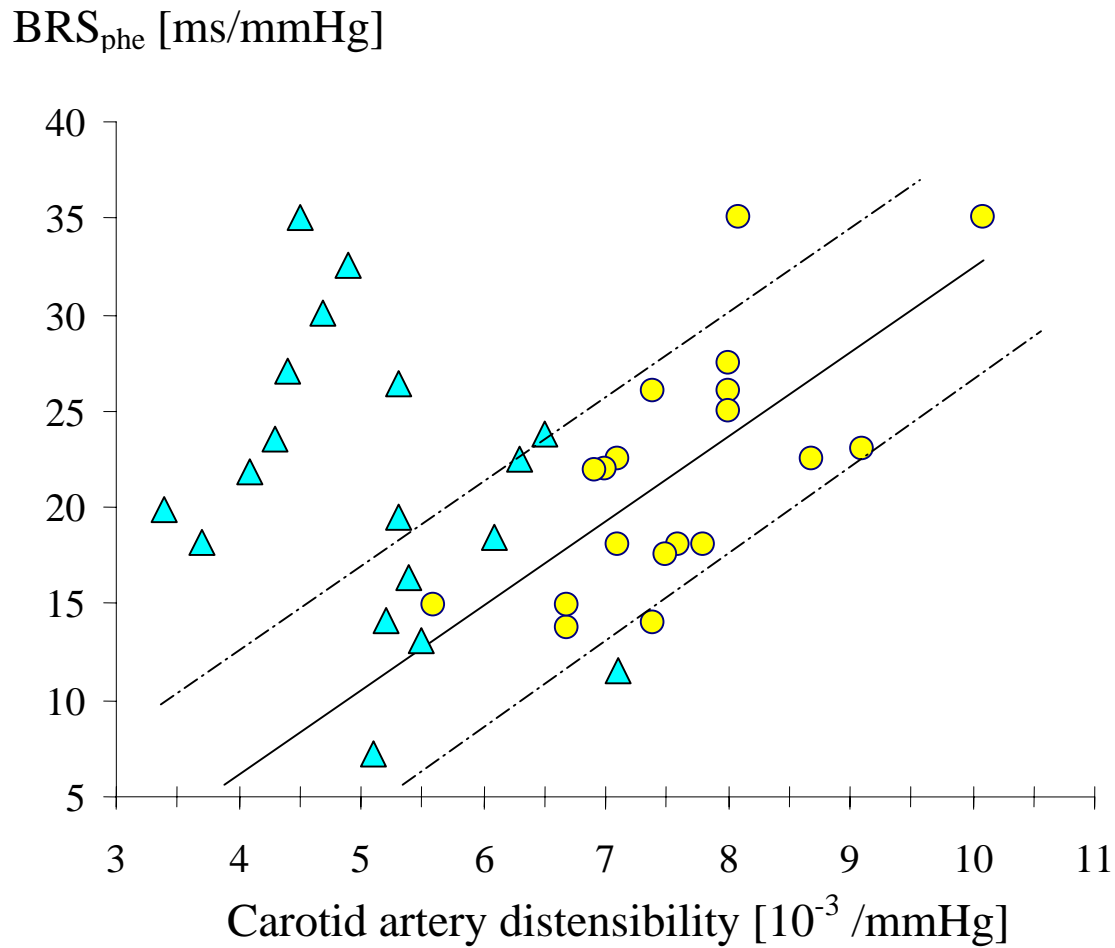
**Table 1: Clinical characteristics, carotid artery dimensions and elastic variables of TGA- patients and control subjects**

BMI – body mass index; SBP – systolic brachial pressure; DBP – diastolic brachial pressure; MBP – mean brachial pressure; HR – heart rate; D – carotid end-diastolic diameter; ΔD – pulsatile distension; DC – distensibility coefficient. Groups were compared for differences by Student's t-test or the Mann–Whitney rank-sum for data failing tests of normality. Data are given as means ± SD. \*significantly different from control at  $p < 0.05$ .

	Patients	Controls
NNSD[ms]	77.3 ± 39.6	66.6 ± 25.0
RMSSD[ms]	76.2 ± 55.7	61.5 ± 37.7
pNN50[%]	28.7 ± 21.3	27.3 ± 21.4
HF[ms <sup>2</sup> ]	2027 ± 2620	1625 ± 2139
LF[ms <sup>2</sup> ]	1733 ± 1560	1029 ± 679
BRS <sub>seq</sub>	20.3 ± 14.7	21.7 ± 12.7
LF <sub>gain</sub>	13.1 ± 9.2	10.6 ± 4.5

**Table 2: HRV and spontaneous BRS-indices of TGA-patients and control subjects**

NNSD – standard deviation of RR-intervals; RMSSD – root mean square of successive RR-interval differences; pNN50 – percent of RR-intervals, which differ more than 50 ms; HF – high (0.15–0.4) frequency power of RR-interval variability; LF – low (0.05–0.15) frequency power of RR-interval variability; BRS<sub>seq</sub> – baroreflex sensitivity determined by the sequence method; LF<sub>gain</sub> – cross-spectral transfer function in the low frequency band. No significant differences were found at  $p < 0.05$ , when groups were compared for differences by Student's t-test or the Mann–Whitney rank-sum for data failing tests of normality. Data are given as means ± SD.



**Fig. 1: Baroreflex sensitivity determined by phenylephrine (BRS<sub>phe</sub>) is directly related to carotid distensibility in controls (circles,  $r = 0.71$ ,  $p < 0.05$ ) but no relation exists in TGA patients (triangles).**