Maturation of Cardiovagal Autonomic Function From Childhood to Young Adult Age

Zsuzsanna Lenard, MD; Peter Studinger, MD; Beatrix Mersich, MD; Laszlo Kocsis, MD; Mark Kollai, MD, PhD

Background—Cardiovagal autonomic control declines with age in adult subjects, which is related in part to increasing stiffness of the barosensory vessel wall. It is not known, however, whether autonomic function changes with age in children.

Methods and Results—We studied 137 healthy subjects divided into 4 age groups: group 1, 7 to 14 years; group 2, 11 to 14 years; group 3, 15 to 18 years; and group 4, 19 to 22 years. Brachial artery pressure was measured by sphygmomanometry and continuous radial artery pressure and carotid artery pulse pressure (ΔP) by applanation tonometry. The R-R interval was derived from the ECG. Autonomic function was assessed by spontaneous sequence and frequency-domain indices, which indicate the extent of coupling between fluctuations in heart rate and systolic pressure. Carotid artery diastolic diameter (DD) and pulsatile distension (ΔD) were measured by echo wall tracking; carotid compliance coefficient (CC) was defined as ΔD/ΔD · distensibility coefficient as 2ΔD/DD · ΔP. From group 1 to group 3, spontaneous indices increased significantly (18.1±1.7 versus 33.3±4.0; 14.4±1.1 versus 25.5±22; 12.9±1.1 versus 20.8±2.0; and 6.4±0.6 versus 16.2±1.4 ms/mm Hg [mean±SEM] for Seq+, Seq−, LFα, and LF gain, respectively), with no significant changes afterward. CC and DC were inversely proportional to age (r=−0.49 and −0.62, respectively, P<0.001). The efficiency of neural integrative mechanisms, estimated as the ratio of spontaneous indices and CC, more than doubled from group 1 to group 3. Spontaneous indices were linearly related to measures of cardiac vagal activity.

Conclusions—The increase in spontaneous indices from early childhood to adolescence, despite gradual stiffening of the carotid artery, may indicate improved cardiovagal autonomic function, which is most likely a result of maturation of neural mechanisms, attaining peak level at adolescence. (Circulation. 2004;110:2307-2312.)

Key Words: vagus nerve ■ nervous system, autonomic ■ baroreceptors ■ aging ■ carotid arteries

Cardiovagal autonomic function declines with age during the adult years, which is partly because of gradual impairment of baroreflex function.1 It has been established by a number of investigators that cardiovagal baroreflex sensitivity (BRS) starts to decline from the 20s and is reduced to almost zero in the 70s and 80s.2-4 The baroreflex becomes functional late in gestation, and its sensitivity then increases gradually, but in the neonate, it is still much below the level that has been reported for young adults.5,6 There are no data in the literature about cardiovagal autonomic function between infancy and young adulthood. This lack of information is surprising, because this is an important period of life, when children increase their physical activities, face intellectual challenges at school, and undergo profound hormonal changes associated with puberty. Physical activity, mental stress, and sexual steroids are factors known to affect autonomic function in the adult, but how these factors exert their influence in children is not known.7-10 It seems reasonable to assume that the efficiency of autonomic neural integration increases from infancy to young adulthood, but this assumption needs to be tested, its mechanism determined, and the time course of changes defined. Autonomic function data obtained from healthy children might serve as reference values for autonomic studies performed on young patients with cardiovascular disease.

Cardiovagal autonomic function is importantly related to baroreflex gain, which is in turn influenced by mechanical and neural factors.11 Baroreceptors are stretch-sensitive receptors embedded in the barosensory vessel wall, and their response to pressure-induced stretch is importantly determined by the compliance of the vessel wall.12 A relation between BRS and carotid distensibility has been shown in healthy subjects and in hypertensive patients.13-15 With advancing age, both BRS and carotid compliance were found to decrease, and the reduction in BRS was explained in part by stiffening of the arterial wall.7 It is not known, however, how changes in large-artery compliance influence cardiovagal autonomic function during the childhood years.
Cardiovascular autonomic function encompasses the central integration of afferent inputs and generation of efferent vagal outflow. Basal vagal outflow may be assessed by measuring various indices of heart rate variability (HRV), and autonomic integrative function may be estimated by measuring the extent of coupling between spontaneously occurring parallel fluctuations in arterial pressure and heart period. These spontaneous, noninvasive indices, which include time-domain (sequence method) and frequency-domain (LF, HF) measures, were shown to be moderately but significantly related to baroreflex gain. The aim of this study was, therefore, to investigate the maturation of cardiovascular autonomic function from early childhood to young adulthood and to estimate the contribution of mechanical and neural factors. To this end, we determined spontaneous sequence and frequency-domain indices and measured carotid artery elastic parameters in a population of young subjects, from 7 to 22 years old. Carotid compliance coefficient (CC) was taken as a measure of mechanical factors, and the ratio of spontaneous indices and CC was considered to give an estimate of the effectiveness of neural integrative mechanisms.

Methods

Subjects

In all, 137 healthy volunteers from the age of 7 to 22 years participated in the study. Subjects were divided into 4 age groups: early childhood (group 1: 7 to 10 years old; n=34), preadolescence (group 2: 11 to 14 years old; n=36), postadolescence (group 3: 15 to 18 years old; n=35); and young adulthood (group 4: 19 to 22 years old; n=32). Anthropometric data are given in Table 1. All were nonsmokers, were free of overt autonomic or cardiovascular disease, and were not taking regular medication. All subjects or relatives of the subject gave informed consent, and the local ethics committee approved the study.

Blood Pressure Measurements

Brachial artery pressure was measured by sphygmomanometry. Carotid artery pulse pressure was measured by applanation tonometry (Millar SPT-301), and the tonometer curve was calibrated by use of the internal electric signal and sphygmomanometric measurements. Radial arterial pressure was monitored continuously with an automated tonometric device (Colin CBM-7000, ADinstruments Ltd.

| TABLE 1. Anthropometric and Hemodynamic Parameters in Subjects of 4 Age Groups |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| No.                             | Group 1         | Group 2         | Group 3         | Group 4         |
| Male/female                      | 15/19           | 20/17           | 17/18           | 16/15           |
| Age, y                          | 8.2±0.2         | 12.1±0.2        | 16.3±0.2        | 20.5±0.2        |
| Height, cm                      | 131±1.06        | 156±1.5         | 169±1.2         | 175±1.9         |
| Weight, kg                      | 26±1            | 47±2            | 62±2            | 68±2            |
| DBP, mm Hg                      | 72±2            | 69±2            | 70±2            | 65±2            |
| SBP, mm Hg                      | 111±2           | 115±3           | 120±3           | 115±2           |
| HR, bpm                         | 89±2            | 81±2*           | 66±2†           | 64±2†           |

| No. indicates number of subjects; DBP, brachial diastolic blood pressure; SBP, brachial systolic blood pressure; HR, heart rate. Data are given as mean±SEM. |

| *Significantly different, P<0.01, from group 1; †significantly different, P<0.01, from group 2. |

Carotid Ultrasoundography

Common carotid artery diameter, its change with the arterial pressure pulse, and carotid intima-media thickness (IMT) were measured 1.5 cm proximal to the bifurcation by means of ultrasonography. The ultrasound device consisted of a vessel wall-tracking system combined with a conventional ultrasound scanner (7.5-MHz linear array, Scanner 200 Pie Medical) and has been described in detail previously.

Other Measurements

R-R intervals were measured from R-wave threshold crossings on continuously recorded ECGs, and respiration was recorded with an inductive system (Respitrace System, Ambulatory Monitoring Inc). Breathing rate was paced at 0.25 Hz.

Protocol

Subjects were studied in the morning hours under standardized conditions, in a quiet room at a comfortable temperature. All fasted at least 2 hours before testing and were asked to refrain from strenuous exercise or drinking alcohol or caffeine-containing beverages for 24 hours before the study. On arrival at the investigation unit, the subjects were equipped with measurement devices and then rested supine for about 15 minutes until the absence of evident heart rate and mean blood pressure trends demonstrated that satisfactory baseline conditions had been achieved. They were asked to synchronize their respiratory rate with a metronome beating at 0.25 Hz. RR interval (RRI) and radial artery pressure was recorded continuously for a 10-minute period to determine spontaneous sequence and time-domain indices. Then, carotid artery tonometric pressure on the right side, diameter, and wall thickness on the left side were recorded simultaneously in 5 epochs, each containing 4 to 8 distension pulses; these recordings were used to determine carotid elastic parameters.

Data Analysis

Spontaneous Indices

The coupling between spontaneous fluctuations in heart rate and systolic pressure was determined by the sequence method and also by spectral analysis calculating the α coefficient (LFα) and the cross-spectral transfer function (LF_spectran) in the low-frequency range. All analog signals were digitized and analyzed with the WinCPRS program (Absolute Alensi Oy) with a sampling rate of 500 Hz and stored in a personal computer for subsequent offline analysis. The software detected the ECG R wave and computed RRI and radial artery systolic blood pressure (SBP) time series and identified spontaneously occurring sequences in which SBP and RRI concurrently increased or decreased over 3 or more consecutive beats. Minimal accepted change was 1 mm Hg for SBP and 5 ms for RRI. Sequence indices were calculated from up-up (Seq+) and down-down (Seq−) sequences as the slope of the regression line between SBP and RRI. Only sequences with a correlation coefficient >0.85 were considered. To determine spectral indices, the signals were interpolated and resampled at the mean heart rate, and their power spectra were determined using fast Fourier transform–based methods. The mean value of the α function (the square root of the ratio of the spectral powers of RRI and SBP), considering only those frequency components in the low-frequency band (LF: 0.05 to 0.15 Hz) where the coherence was >0.5, was taken as the α coefficient (LFα). Cross-spectral transfer function (LF_spectran) was calculated by dividing the cross spectra of the 2 signals by the power spectra of the input signals.

Heart Rate Variability

Time- and frequency-domain measures of HRV were used to assess the level of cardiac vagal activity (CVA). From 10-minute recordings of RRI, HRV indices were calculated by use of the WinCPRS program: the standard deviation of RRI (NNSD), the root mean square of successive differences (RMSSD), the percentage of successive RRI that differed by <50 ms (pNNS0), and LF (0.05 to 0.15 Hz) and high-frequency (0.15 to 0.4 Hz) power of R-R interval variability.
Carotid Artery Elastic Parameters

Carotid artery strain was assessed as $\Delta D/\Delta D$, where $\Delta D$ and $\Delta D$ represent pulsatile distension and end-diastolic diameter, respectively. Compliance (CC) and distensibility (DC) coefficients were calculated according to the following formulas:

$\text{CC} = \Delta D/\Delta P$ and $\text{DC} = (\Delta D/\Delta D)/\Delta P$, where $\Delta P$ represents carotid artery pulse pressure. Carotid artery lumen cross-sectional area (LCSA) and intima-media cross-sectional area (IMCSA) were calculated as

$LCSA = \pi (DD/2)^2$ and $\text{IMCSA} = \pi (DD/2+\text{IMT})^2 - \pi (DD/2)^2$. Incremental elastic modulus was determined as $E_{\text{inc}} = [3(1+\text{LCSA/IMCSA})]/\text{DC}$. Diameter and pressure data obtained during the recording epochs were averaged to give a mean value for each subject.

Statistical Analysis

Data are expressed as mean±SEM. Differences between age groups were analyzed by 1-way ANOVA and post hoc Tukey test. Sex differences in different age groups were analyzed by 2-way ANOVA and post hoc Tukey test. Relationships between variables were determined by simple linear regression 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

Subjects in all age groups maintained the 0.25-Hz respiratory rate to the extent that no differences existed in mean respiratory rates between groups. Hemodynamic data are given in Table 1. From group 1 to group 4, heart rate was decreasing, and brachial systolic pressure showed a tendency to increase and diastolic pressure to decrease, resulting in significant increases in pulse pressure. Similar changes were observed in carotid and radial artery pressures as well.

Spontaneous sequence and frequency-domain indices exhibited characteristic changes with age (Figure 1, top, and Table 2). None of them changed significantly from group 1 to group 2, but all increased markedly in group 3. Time-domain indices declined slightly in group 4, whereas frequency-domain indices remained unchanged. With increasing mean values, variability increased as well. When we adjusted the various spontaneous indices to the mean R-R interval in the individual subjects, the differences between mean values of groups 2 and 3 were somewhat reduced but remained significant. No difference was found between female and male subjects in spontaneous indices.

Carotid artery systolic and diastolic diameter exhibited a continuous, gradual increase from group 1 to group 4, whereas pulsatile distension did not change (Figure 2). Consequently, carotid pulsatile strain decreased. Reduction in pulsatile strain, associated with increased carotid pulse pressure, resulted in substantial decrease in carotid artery CC and DC ($\approx 30\%$ and $40\%$, respectively), whereas $E_{\text{inc}}$ more than doubled (Figure 1, middle, and Table 3). CC and DC were inversely and $E_{\text{inc}}$ directly proportional with age ($r=-0.49, -0.62$, and $+0.61$, respectively; $P<0.001$). No sex difference was observed in elastic variables.

The increase in spontaneous indices, despite decreasing CC, indicated increased efficiency of neural integrative mechanisms. To obtain a quantitative estimate of the neural component, we calculated the ratio of various spontaneous indices and CC for each subject. The bottom panel of Figure 1 illustrates age-related changes in the $\text{LF}_{\text{gain}}/\text{CC}$ ratio, using other spontaneous indices for the numerator produced similar results. Changes in these ratios followed a pattern similar to that observed in spontaneous indices but were more accentuated.

Time- and frequency-domain HRV indices are given in Table 2. They exhibited no change from group 1 to group 2, increased in group 3, and declined in group 4. Changes were significant for NNSD, LF, and high frequency ($P<0.05$) and approached significance in the case of RMSSD and pNN50 ($P=0.09$ and 0.07, respectively). Changes in spontaneous and HRV indices were similar in that both measures attained peak value in group 3, and spontaneous and HRV indices were linearly related across subjects (Figure 3). The correlation coefficients for relations between various spontaneous and HRV indices ranged between $r=0.41$ and $r=0.75$; all relations being significant at the $P<0.001$ level.

Discussion

In this study, we investigated the maturation of cardiovagal autonomic function within the age period of 7 to 22 years and found that spontaneous indices increased and attained maximum value at adolescence. The mechanism by which autonomic function improves with maturation is not clear and may be related to both mechanical and neural alterations with age.
TABLE 2. Time- and Frequency-Domain Spontaneous Indices and Measures of CVA in Subjects of 4 Age Groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seq+, ms/mm Hg</td>
<td>18.1±1.7</td>
<td>20.5±1.6</td>
<td>33.3±4.0†</td>
<td>25.6±2.4*</td>
</tr>
<tr>
<td>Seq−, ms/mm Hg</td>
<td>14.4±1.1</td>
<td>16.5±1.3</td>
<td>25.5±2.2†</td>
<td>19.9±1.6*</td>
</tr>
<tr>
<td>LF, ms/mm Hg</td>
<td>12.9±1.1</td>
<td>12.9±1.0</td>
<td>20.8±2.0†</td>
<td>21.5±1.6†*</td>
</tr>
<tr>
<td>LFgain, ms/mm Hg</td>
<td>6.4±0.6</td>
<td>8.1±0.7</td>
<td>16.2±1.4†</td>
<td>15.1±1.3†*</td>
</tr>
<tr>
<td>NNSD, ms</td>
<td>64±4</td>
<td>61±4</td>
<td>81±6†</td>
<td>72±5</td>
</tr>
<tr>
<td>RMNSSD, ms</td>
<td>64±6</td>
<td>55±5</td>
<td>77±8</td>
<td>70±7</td>
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<tr>
<td>pNN50, %</td>
<td>28±3</td>
<td>26±4</td>
<td>38±4</td>
<td>37±5</td>
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<tr>
<td>LF, ms²</td>
<td>1011±122</td>
<td>928±118</td>
<td>1653±267‡</td>
<td>1186±214</td>
</tr>
<tr>
<td>LFnu, %</td>
<td>42.8±2.9</td>
<td>44.1±3.2</td>
<td>43.6±3.0</td>
<td>40.2±2.7</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>1559±332</td>
<td>1410±254</td>
<td>2858±540‡</td>
<td>1692±308</td>
</tr>
<tr>
<td>HFnu, %</td>
<td>56.1±3.4</td>
<td>53.5±3.3</td>
<td>54.9±3.0</td>
<td>59.1±3.2</td>
</tr>
</tbody>
</table>

Seq+ indicates spontaneous sequence index calculated from up-up sequences; Seq−, spontaneous sequence index calculated from down-down sequences; LFnu, coefficient in the low-frequency range; LF gain, cross-spectral transfer gain in the low-frequency range; NNSD, SD of RR intervals; RMSSD, root mean square of successive RR-interval differences; pNN50, percentage of RR intervals that differ >50 ms; LF, low-frequency (0.05–0.15 Hz) power of RR-interval variability; LFnu, normalized low-frequency (0.05–0.15 Hz) power of RR-interval variability; HF, high-frequency (0.15–0.4 Hz) power of RR-interval variability; HFnu, normalized high-frequency (0.15–0.4 Hz) power of RR-interval variability. Data are given as mean±SEM.

*pSignificantly different, P<0.002, from group 1; †Significantly different, P<0.002, from group 2; ‡Significantly different, P<0.05, from group 2.

Arterial distensibility influences the transduction of pressure into changes in barosensory vessel diameter. Greater distensibility of the vessel wall results in increased strain for the baroreceptor; conversely, stiffening of the wall “splints” the receptors. Stiffening of the large elastic arteries with age has been demonstrated in a number of studies, and it is generally agreed that stiffening of the barosensory vessel wall accounts to a large extent for the age-related decline in autonomic sensitivity. Earlier reports have indicated that the carotid artery starts to stiffen already at younger ages, and our present data, demonstrating considerable reduction in both carotid CC and DC throughout the observation period, fully confirm these earlier findings. Einc also increased without concomitant changes in IMT, possibly indicating altered elastic properties of the carotid artery wall material. In summary, it may be concluded that changes in carotid artery biomechanics cannot explain the increase in spontaneous indices. We found no sex-related differences in carotid artery elasticity, which is in line with one earlier observation. Sex differences in large-artery elastic function represents a controversial issue. In one study, the carotid artery was found to be stiffer in 15- to 70-year-old men than women, whereas in another study, the opposite was demonstrated in prepubertal children, which difference then disappeared after puberty.

Our observation that spontaneous indices increase from childhood to adolescence despite stiffening of the carotid artery suggests that the efficiency of neural integrative mechanisms is enhanced and more than compensates for the reduced baroreceptor activation. Our present data do not answer the question of which neural mechanisms might be improving during autonomic maturation. There are no data in the literature that would indicate increased baroreceptor output during early ontogeny; rather, baroreceptor strain sensitivity was found to decline shortly after birth. Although

Figure 2. Representative recordings of carotid artery distension waveforms obtained from subjects of 4 different age groups.
central autonomic function is difficult to study in humans, as far as the cardiovascular autonomic function is concerned, the level of CVA may serve as an indicator of the efficiency of central parasympathetic signal processing. CVA was reported to increase during early ontogeny, to reach peak value at adolescence, and then to decline with advancing age.\textsuperscript{33,34} Our present data confirm these earlier findings. Although baroceptor afferents provide the main facilitatory input to cardiac vagal motoneurons, activation is received from other sources as well.\textsuperscript{1} CVA was shown to be related to autonomic sensitivity,\textsuperscript{35} but the relationship may be indirect, and recently a common central neuronal mechanism was suggested to influence BRS and CVA independently of each other.\textsuperscript{36}

Regardless of the actual organization of central parasympathetic circuitry, our present observation that age-related changes in spontaneous indices and CVA are directly proportional suggests that central parasympathetic signal processing may play a role in the maturation of cardiovascular autonomic function. Age-related changes in parasympathetic neuroeffector mechanisms represent a controversial issue. Some data indicate that sinoatrial node responsiveness is altered in adults with age, whereas others do not.\textsuperscript{37,38} No data are available, however, on the maturation of neuroeffector function in children. It should be noted that maturation of certain somatic nervous system functions also occurs at puberty. Walking rhythm and gait control were shown to reach their highest level of functional organization at \textasciitilde 14 years of age.\textsuperscript{39}

It remains to be established what sort of influence might induce the improvement in neural autonomic control at adolescence. Genetic factors, hormonal status, and changes in physical activity are possible candidates. A recent twin study found that BRS is strongly influenced by genetic variance in the normal human.\textsuperscript{40} Also, normotensive subjects with a family history of hypertension exhibited a decrease in baroreflex function compared with normotensives without a family history of hypertension.\textsuperscript{41} Hormonal factors might also play a role in the maturation of autonomic function, because the marked increase in spontaneous indices that we found in the present study coincides with the increase in plasma sexual steroid level that occurs at puberty. Both estrogens and androgens were found to increase BRS experimentally,\textsuperscript{3,10} which is in line with our present observation that increases in spontaneous indices occurred in both males and females. The influence of sex on baroreflex function is unclear, and the method of measurement of BRS may contribute to different outcomes. When male and female subjects 20 to 80 years old were studied by use of dynamic pressure elevations with the phenylephrine bolus method, BRSs of males were found to be higher than those of females.\textsuperscript{42,43} However, when the pressor response developed slowly with the infusion method, the heart rate response was similar in both sexes.\textsuperscript{44} Because the heart rate response to abrupt pressure stimuli reflects primarily the activity of the vagal component, vagal activation seems to play a smaller role in the baroreflex-mediated bradycardia in females. We, in the present study, and other investigators earlier, could not demonstrate sex-related differences in spontaneous indices, which might be explained by the slowly developing nature of spontaneous fluctuations in arterial pressure.\textsuperscript{3} Aerobic physical exercise training was shown to affect both baroreflex function and CVA favorably and to prevent the age-related decline in BRS.\textsuperscript{7,41} Recent reports suggest that exercise training may influence both central autonomic activity and arterial compliance.\textsuperscript{7,38} In these studies, however, the influence of physical exercise was studied only in adult subjects, and it is not known to what extent these mechanisms are operational in children.

Conclusions

In this study, we demonstrated in healthy subjects 7 to 22 years old that (1) spontaneous indices increase with age, exhibiting a marked increase at adolescence; (2) carotid artery elasticity decreases with age, exhibiting continuous gradual decline; and (3) changes in CVA and in spontaneous indices are directly proportional. We conclude that neural autonomic mechanisms mature in school-age children attaining peak level at adolescence. Because spontaneous indices are strongly related to basal vagal outflow, and this is importantly related to baroreflex gain, the observed differences may reflect alterations in the baroreflex arc.

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References

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