THE EFFECT OF AGING ON CARDIAC AUTONOMIC AND POSTGANGLIONIC SUDOMOTOR FUNCTION

PHILLIP A. LOW, MD FRACP, TONETTE L. OPPER-GEHRKING, CAROL J. PROPER, and IRVIN ZIMMERMAN, MSEE

Cardiovascular tests of autonomic function are performed extensively since the procedures are straightforward, reproducible and noninvasive. The heart rate (HR) response to deep breathing (HR_{DB}) and the Valsalva ratio (VR) are the most widely used tests.

HR_{DB} is generally accepted as being age-dependent, while it has been suggested that VR is non-age-dependent. Some of the controversy exists because of conclusions drawn from small numbers of subjects of an inadequate age range and the lack of standardization. We studied 157 control subjects, aged 10-83 years, using standardized methods. Since some variability may also be related to the neural system tested (the HR_{DB} and VR utilize long afferent and efferent pathways and results may also be affected by alterations in the central processing unit or effector cell), we also studied the effect of age on the quantitative sudomotor axon reflex sweat test (QSART), which involves a much shorter neural pathway (the distal postganglionic sympathetic sudomotor axon).

METHODS

Subjects. All studies on human subjects had received prior approval of the Mayo Institutional Review Board. The HR_{DB} and VR responses were studied in 157 healthy subjects aged 10-83 years. There were 81 females and 76 males. Excluded from analyses were 2 Valsalva maneuver recordings and 35 from HR_{DB} determinations because of the imperfect technical quality of the recordings or due to missing values.

We studied the QSART response in 139 normal subjects aged 10-83 years. Seventy-four were females and 65 were males; 114 were technically suitable for quantitation.

Autonomic Tests. All studies were performed in the Autonomic Reflex Laboratory with the subject supine and rested. The room was temperature (23°C) and humidity controlled. HR_{DB} and VR were obtained as previously described. In brief,
the subject was connected to an electrocardiographic monitor (Saturn 3, Spacelabs Inc, Chatsworth, CA) and in turn to a microprocessor which had an operator selectable threshold setting for detecting the QRS complex. This output was processed by an IBM PC-XT computer via an analog to digital board. The subject breathed deeply at a rate of 6/minute. Eight cycles were recorded. The five largest responses were read from the computer using a cursor, averaged and the HR range (maximum—minimum) derived. Bennett et al.5 considers the first response, which is often larger, preferable to an averaged value. With continued hyperventilation there is hypocarbia,4,15 with inhibition of sinus arrhythmia. There is also some variability among individual responses, and some responses are marred by artifact or ectopic beats. Based on these considerations, we have standardized our testing by routinely recording eight cycles and determining the mean of the five largest responses. We find this approach preferable to the mean of all or the last few responses.

For VR, the subject, rested and recumbent, was asked to maintain a column of mercury at 40 mmHg (not exceeding 50 mmHg), for 15 seconds via a bugle with an air leak (to ensure an open glottis). The responses were obtained in triplicate and the largest response was accepted. The VR was derived from the maximum HR generated by the Valsalva maneuver divided by the lowest HR occurring within 30 seconds of peak HR.9,21 The choice of 40–50 mmHg was made since a pressure of 40 mmHg seems to yield reproducible results while the VR below 20 mmHg is inadequate and above 60 mmHg results in less reproducibility.20

The methodology for QSART has been detailed.22,23 In brief, a population of eccrine sweat glands is stimulated by the iontophoresis of 10% acetylcholine using a constant current generator (Mayo Section of Engineering) and a stimulus of 2 mA for 5 minutes. Impulses pass antidromically along sympathetic C fibers to a branch point then orthodromically along other sympathetic C fibers to evoke a sweat response with a latency of 1–2 minutes. Sweat output from a different compartment is evaporated off by a stream of nitrogen gas of low constant humidity and controlled flow rate and measured by a sudorimeter (Demco Research and Development, Lansing, MI). The sweat response returned to baseline within 5–10 minutes of completion of the stimulus. The recording was continued for 5 minutes beyond the stimulus, after which time the area under the curve was integrated by our computer and the response was displayed as sweat output in microliters/square centimeters. The response was recorded over the medial forearm (25% of the distance from the pisiform bone to the ulnar epicondyle) and the proximal left foot (over the extensor digitorum brevis muscle).

RESULTS

Parasympathetic Function. HRDB was studied in 122 subjects and was found to be not significantly different between the sexes. The data was, therefore, combined (Fig. 1). A consistently significant regression with age was found. For response to deep breathing (y = heart rate range in bpm and x = age in years):

\[ y = 37.17 - 0.36x; R = 0.7; P < 0.001. \]

VR, studied in 155 subjects, also showed no sex difference, and the data, therefore, was combined (Fig. 2). For VR (y = Valsalva ratio and x = age in years):

\[ y = 2.27 - 0.01x; R = 0.5; P < 0.001. \]

Sudomotor Function. Mean (±SD) sweat output was 3.01 µL/cm² and 1.15 µL/cm² for the forearm of males and females, respectively. This difference was highly significant (P < 0.001). The corresponding values for the foot were 2.65 ± 1.65 and 1.15 ± 1.14 µL/cm² for males and females, respectively. The difference was, again, statistically significant (P < 0.001). Thus, the two groups were considered separately. For the forearm the

\[ Y = 37.17 - 0.36X \]

\[ R = 0.7 \]
QSART response did not regress with age. For the foot response there was a consistent negative slope of QSART responses with increasing age which reached statistical significance for females only (Figs. 3 and 4).

DISCUSSION

The main finding of the present study is that there is a substantive negative regression of both HRDB and VR which is suggestive of an impairment of parasympathetic activity with increasing age. In contrast, the age-related changes for QSART were relatively minor. HRDB is a particularly useful test of parasympathetic function since the pathways appear to be mainly vagal. The efferent pathway is clearly vagal since sinus arrhythmia ceases following administration of atropine or inactivation of vagal efferents. Controversy exists as to the relative importance of pulmonary stretch receptors (Hering-Breuer reflex), the Bainbridge reflex, baroreflex sensitivity, and central irradiation of impulses from the respiratory to cardioinhibitory centers. During inspiration, pulmonary stretch receptors are activated and impulses travel up the vagus nerve to cause inhibition of the respiratory center. This reflex is called the Hering-Breuer respiratory reflex. From the respiratory center, there is irradiation of impulses which results in inhibition of the cardioinhibitory center. Impulses then travel via the vagus nerve to the sinoatrial node resulting in an increase in HR. However, pulmonary receptors have been suggested to be less important in humans.

Increased venous return during inspiration with resultant atrial distension is likely to be important for at least 2 reasons. First, it activates the Bainbridge reflex. Distension of the right atrium and great veins stimulates an increase in HR. The pathway is likely right atrium → vagus nerve → nucleus of tractus solitarius → vagus → sinoatrial (SA) node. The normal function of this reflex is probably to handle the increase in venous return. Second, this increased intraatrial pressure results in direct pressure on venoatrial mechanoreceptors in the vicinity of the SA node. The vasomotor center is stimulated via vagal afferents. From here, sympathetic efferents travel down the spinal cord to the intermediolateral column, then via preganglionic and postganglionic cardiac sympathetic pathways which supply the SA node to increase HR. Brooks et al. showed, in the anesthe-
tized dog, that stretch in the region of the SA node resulted in cardioacceleration, even following atropine.

There is also a baroreflex contribution. Eckberg et al.\textsuperscript{8} found that baroreflex sensitivity is greatest during late inspiration and early expiration but that the oscillation in sensitivity is not due to interference by respiratory neuronal activity. Melcher\textsuperscript{26} suggested that sinus arrhythmia maybe due to a cardiocardiac reflex with central resetting of the baroreflex, although some controversy regarding this proposal exists.\textsuperscript{8}

The main origin of respiratory sinus arrhythmia has been suggested as being the medullary connection from the respiratory to the cardioinhibitory center since there is cessation of vagal different activity during the inspiratory phase of natural but not artificial ventilation.\textsuperscript{17,19} Patients with brain stem infarction lose their sinus arrhythmia.\textsuperscript{29} Sinus arrhythmia also ceases with hypocarbia and deep anesthesia.\textsuperscript{4,15} However the relative importance of central irradiation in humans is uncertain.\textsuperscript{26}

All studies to date involving large numbers of normal subjects have revealed a progressive reduction in the HR response to deep breathing with increasing age\textsuperscript{3,6,9,11,12,23,25,27,29,31,32,37,38} (Table 1). Some studies disclosed a linear relationship to age with slopes of 0.34–0.41,\textsuperscript{12,16,25} values similar to ours. Others reported a similar slope but expressed the data in logarithmic format. Some studies did not reveal an age effect,\textsuperscript{7,14,36} but these were usually confined to a small age range (Table 1). Kajer and Sachs\textsuperscript{18} reported a reduction in the HR response with age but only in subjects older than 60 years.

The effect of age on HR response to VR is controversial (Table 2). Some workers have re-

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>No. of subs.</th>
<th>Age range</th>
<th>Duration of test</th>
<th>Cycles/min</th>
<th>Position</th>
<th>Effect of age and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>Wheeler &amp; Watkins</td>
<td>25</td>
<td>20–50</td>
<td>1 min</td>
<td>6</td>
<td>Supine</td>
<td>SA blocked by atropine; age effect present</td>
</tr>
<tr>
<td>1976</td>
<td>Hellman &amp; Stacy</td>
<td>24</td>
<td>21–65</td>
<td>2 min</td>
<td>6</td>
<td>Sitting</td>
<td>Slope = –0.35</td>
</tr>
<tr>
<td>1978</td>
<td>Bennett et al.</td>
<td>31</td>
<td>18–60</td>
<td>? 1 min</td>
<td>6</td>
<td>Supine</td>
<td>Uncertain</td>
</tr>
<tr>
<td>1979</td>
<td>Sundkvist et al.</td>
<td>25</td>
<td>&lt;50</td>
<td>1 min</td>
<td>5</td>
<td>Supine</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>1979</td>
<td>Hilsted &amp; Jensen</td>
<td>10</td>
<td>20–40</td>
<td>1 min</td>
<td>5</td>
<td>Supine</td>
<td>No effect but narrow range</td>
</tr>
<tr>
<td>1980</td>
<td>Watkins &amp; Mackay</td>
<td>54</td>
<td>20–49</td>
<td>1 min</td>
<td>6</td>
<td>Supine</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>1981</td>
<td>Dyrberg et al.</td>
<td>28</td>
<td>30–48</td>
<td>1 min</td>
<td>6</td>
<td>Supine</td>
<td>Uncertain</td>
</tr>
<tr>
<td>1982</td>
<td>Pfeifer et al.</td>
<td>22</td>
<td>47 ± 3</td>
<td>6 min</td>
<td>5</td>
<td>Supine</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>1982</td>
<td>Smith</td>
<td>174</td>
<td>16–69</td>
<td>1 min</td>
<td>5</td>
<td>Supine</td>
<td>? Decline with age</td>
</tr>
<tr>
<td>1982</td>
<td>Weiling et al.</td>
<td>133</td>
<td>10–65</td>
<td>1 min</td>
<td>6</td>
<td>Supine</td>
<td>10–29; 20 bpm</td>
</tr>
<tr>
<td>1983</td>
<td>Persson &amp; Solders</td>
<td>75</td>
<td>21–70</td>
<td>1 min</td>
<td>6</td>
<td>Supine</td>
<td>Progressive red with age R – R = –0.0007 × age + 0.072</td>
</tr>
<tr>
<td>1983</td>
<td>Pfeifer et al.</td>
<td>103</td>
<td>19–82</td>
<td>5 min</td>
<td>5</td>
<td>Supine</td>
<td>Log-Linear red with age</td>
</tr>
<tr>
<td>1985</td>
<td>Oikawa et al.</td>
<td>162</td>
<td>4–77</td>
<td>2 min</td>
<td>6</td>
<td>Supine</td>
<td>Decrease with age</td>
</tr>
<tr>
<td>1985</td>
<td>Ewing et al.</td>
<td>71</td>
<td>16–65</td>
<td>?</td>
<td>6</td>
<td>Sitting</td>
<td>Decrease above age 60</td>
</tr>
<tr>
<td>1985</td>
<td>Kajer &amp; Sachs</td>
<td>52</td>
<td>20–80</td>
<td>10 cycles</td>
<td>6</td>
<td>?Sitting</td>
<td>HRV = 41.1 – 0.46 × age</td>
</tr>
<tr>
<td>1986</td>
<td>Masaoka et al.</td>
<td>143</td>
<td>20–80</td>
<td>1 min</td>
<td>6</td>
<td>Supine</td>
<td>&gt;25 bpm</td>
</tr>
<tr>
<td>1986</td>
<td>Low et al.</td>
<td>35</td>
<td>10–30</td>
<td>1 min</td>
<td>6</td>
<td>Supine</td>
<td>&gt;18 bpm</td>
</tr>
<tr>
<td>1986</td>
<td>Solders</td>
<td>128</td>
<td>40–74</td>
<td>1 min</td>
<td>6</td>
<td>Supine</td>
<td>Add 53 pts</td>
</tr>
<tr>
<td>1986</td>
<td>O’Brien et al.</td>
<td>310</td>
<td>18–85</td>
<td>10 secs</td>
<td>1</td>
<td>Sitting</td>
<td>Decrease with age</td>
</tr>
<tr>
<td>1986</td>
<td>Gautschy et al.</td>
<td>120</td>
<td>22–92</td>
<td>1 min</td>
<td>6</td>
<td>Sitting</td>
<td>Decrease with age</td>
</tr>
<tr>
<td>1986</td>
<td>Vita et al.</td>
<td>70</td>
<td>25–71</td>
<td>&lt;1 min</td>
<td>6</td>
<td>Sitting</td>
<td>Reduced with age</td>
</tr>
<tr>
<td>1986</td>
<td>Bergstrom et al.</td>
<td>56</td>
<td>16–59</td>
<td>1 min</td>
<td>6</td>
<td>Supine</td>
<td>Decrease with age</td>
</tr>
<tr>
<td>1986</td>
<td>Clark &amp; Mapstone</td>
<td>85</td>
<td>31–92</td>
<td>1 min</td>
<td>6</td>
<td>Sitting</td>
<td>Decrease with age</td>
</tr>
</tbody>
</table>
reported a lack of variability with age, while others have observed a difference. The slopes reported have been similar. Ingall reported a slope of 0.1, which is identical to ours. Part of the problem can be related to a lack of standardization. Patients are studied sitting in some protocols and supine in others. The duration of the maneuver has varied between 10 and 20 seconds and the effort has also varied (Table 2). A problem encountered beyond standardization is the inability to measure the true stimulus. The tachycardia is due to vagal release and sympathetic activation in response to a lowering in BP as a result of a reduction in venous return in phase II of the maneuver. The bradycardia is in response to the BP overshoot in phase IV. The moment to moment BP responses are not measured and the actual stimulus may be different in various subjects who perform the same maneuver. It is clear from the present study that there is a clear age-related impairment of the VR.

The QSART response is thought to be mediated by an axon reflex involving postganglionic sympathetic sudomotor fibers and their effector, the eccrine sweat gland. While there are considerable differences in sweat volume depending on sex, less impressive impairments are observed with increasing age. There is a reduction with age but there are also some elderly subjects who exhibit large sudomotor responses so that the slope reached significance only in females.

It appears clear that the effect of age on the autonomic nervous system is complex, depending on the system tested, the site examined, and the particular test used.

**REFERENCES**


20. Levin AB: A simple test of cardiac function based upon the heart rate changes induced by the Valsalva maneuver. Am J Cardiol 1966;18:90–99.


