Adrenergic and Vagal Baroreflex Sensitivity in Autonomic Failure

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Background: The baroreflex is responsible for maintaining a stable blood pressure (BP) despite changes in body position. The baroreflex regulates BP by changing the heart rate (vagal component) and total peripheral resistance (adrenergic component). Baroreflex sensitivity is widely used to quantify the vagal component of the reflex, but the adrenergic component is not quantifiable in the autonomic laboratory.

Objectives: To develop and validate an index of adrenergic baroreflex sensitivity.

Design: We validated this index with microneurographically recorded muscle sympathetic nerve discharges generated by the Valsalva maneuver and verified it against groups of patients with graded severities of adrenergic failure.

Results: Adrenergic baroreflex sensitivity relates BP recovery time to the preceding decrease in BP evoked by the Valsalva maneuver. This index showed a graded and highly significant impairment in 3 groups of patients, (1) those with orthostatic hypotension (n=26), (2) those with borderline orthostatic hypotension (n=34), and (3) those with impaired reflex vasoconstriction without orthostatic BP change (n=24), when compared with an age- and sex-matched control group (n=29). Adrenergic baroreflex sensitivity better tracked the severity of adrenergic failure than the vagal component of baroreflex sensitivity and provides a much needed index to quantify total peripheral resistance changes in patients with adrenergic failure.

Conclusions: The 2 indices of baroreflex sensitivity separately evaluate the vagal and adrenergic components of the baroreflex. Combined, they provide an index of composite or global baroreflex function.

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METHODS

SUBJECTS

The study was approved by the Mayo Clinic Internal Review Board. We investigated 29 age- and sex-matched healthy control subjects and 84 patients divided into 3 groups, each representing a different severity and distribution of adrenergic autonomic failure. The groups were as follows: (1) patients with OH, with OH defined as an orthostatic reduction in systolic BP (SBP) of 30 mm Hg or higher for at least 50% of head up tilt, being 97.5 percentile or greater of our 270 healthy controls; (2) patients with borderline orthostatic hypotension (BOH), consisting of an orthostatic decrease in SBP of greater than 10 mm Hg but less than 30 mm Hg, indicating an intermediate degree of adrenergic failure; (3) patients with loss of late phase 2 of the VM (2_L), without a decrease in BP, indicating mild adrenergic failure; and (4) an age- and sex-matched control group.

The OH group contained 26 patients (13 men and 13 women; mean ±SD age, 51.4 ± 10.1 years), the BOH group consisted of 34 patients (19 men and 15 women; mean ±SD age, 57.8 ± 14.5 years), the 2_L group included 24 patients (14 men and 10 women; mean ±SD age, 56.0 ± 12.4 years), and the control group contained 29 subjects (13 men and 16 women; mean ±SD age, 51.5 ± 15.3 years). Patients who were unable to maintain an expiratory pressure of at least 30 mm Hg for at least 10 seconds during the VM were excluded from the study. Patients with a flat-top Valsalva response (defined as a response in which the BP response increased above baseline by at least 20 mm Hg for at least 10 seconds) were omitted as well. This resulted in 14 patients with OH, 28 patients with BOH, 19 patients with 2_L, and 29 control subjects for 1 section of the analysis.

We excluded patients with conditions such as cardiac, pulmonary, hepatic, renal, hematologic, and neoplastic disorders, and patients with neurocardiogenic syncope. Patients taking medications known to cause OH or otherwise affect autonomic testing were asked to discontinue use of the drug for 5 half-lives, if such a procedure was not harmful to the well-being of the patient. For patients taking levodopa or carbidopa, the drug was omitted on the day of the study and resumed after the test. No coffee, food, or nicotine was permitted for 4 hours before the study.

In addition, we analyzed the MSNA of 10 previously described subjects: 8 healthy controls and 2 patients diagnosed as having neuropathic orthostatic intolerance. The group contained 5 men and 5 women (mean ±SD age, 32.4 ± 10.8 years). These subjects and patients were selected to provide the necessary full range of change in phases of the VM. To our knowledge, detailed analyses of the MSNA response to different phases of the VM and of their relationship to PRT have not previously been performed on these patients.

PROTOCOL

Heart rate was recorded using a standard 3-lead electrocardiogram (Ivy Biomedical Systems, Inc, Branford, Conn). Arterial BP was continuously measured at the finger usingbeat-to-beat photoplethysmographic recordings (Finapres BP monitor model 2300 and Finometer; Ohmeda, Englewood, Colo). All subjects underwent an autonomic reflex screen to evaluate the severity and distribution of sudomotor, adrenergic, and cardiovagal function. Before the recordings, the subjects lay comfortably for 15 minutes. The subjects then performed 2 cycles of deep breathing (DB), with inspiratory and expiratory cycles of 5 seconds each (6 breaths per minute). To establish a smooth rhythm and to ensure maximal breathing, the subjects were instructed to follow an oscillating bar.

Following another 5 minutes of rest, the subjects were asked to perform the VM. They were instructed to maintain a column of mercury at 40 mm Hg for 15 seconds via a tube with an air leak (to ensure an open glottis). The VM was repeated until 2 like responses were obtained. A baseline of 3 minutes between each test was used.

VARIABLES

Baseline supine HR and systolic, diastolic, and mean arterial BP averages were determined for all patients during a 30-second interval directly preceding the VM. Peak SBP changes from baseline and HR were determined for all phases of the VM. The following variables were then determined for each patient. (1) Adrenergic barosensitivity (BRS_a) was defined as the SBP decrement associated with phase 3 divided by the PRT. The PRT is defined as the interval between the lowest SBP of phase 3 and its return to baseline following the VM. Subjects were excluded if the SBP did not decrease below baseline during phase 3 and, therefore, the PRT could not be calculated. An alternative calculation (BRS_a1) relates PRT to a combined decrease in BP during early phase 2 and 0.75 of phase 3, which exceeds early phase 2. The BRS_a1 is the just described decrease in BP divided by the PRT. (2) Cardiovagal barosensitivity (BRS_v) is expressed as the regression slope of heart period over SBP during early phase 2. (3) The product of BRS_a and BRS_v was calculated as a combined baroreflex response, composing a composite or global measure for baroreflex function (BRS_g). The same calculations were done with BRS_a1 and BRS_v to determine BRS_g1.

In addition, the average HR response to DB, defined as the average of the 5 largest consecutive HR responses to DB, was accepted and used for the analysis. The Valsalva ratio, defined as the ratio between the highest HR reached in phase 2 and the lowest HR of phase 4, was also accepted and used for analysis.

MUSCLE SYMPATHETIC NERVE ACTIVITY

In a second step, we analyzed MSNA responses to VM stimulus. These data had been collected earlier from 10 subjects (8 healthy controls and 2 patients with neuropathic orthostatic intolerance) as part of a larger protocol, which included 3 consecutive VMs for each subject. To our knowledge, the data had not been previously analyzed in this manner. For each patient, MSNA response to early phase 2 and phase 3 was calculated for each of the 3 VMs. The MSNA total activity was calculated as the area under the curve, expressed as a percentage of baseline (ie, each subject’s baseline was set equal to 100%, and MSNA responses were calculated as a percentage of that baseline) using signal processing software (Windaq, Dataq Instruments, Akron, Ohio). In addition, the following variables were calculated for each VM trial (Figure 1): (1) the change in SBP during late phase 2 from the lowest point at the end of early phase 2 to the highest point at the beginning of phase 3; (2) PRT, and (3) BRS_a, as previously described. The relationship was then calculated between MSNA response to early phase 2 and change in SBP during late phase 2. It was also calculated between the combined MSNA responses to early phase 2 and phase 3 and PRT and BRS_a, respectively. For each subject, results to individual VMs were averaged over the 3 trials. The BRS is a slope function, and PRT is the time taken for the BP to return to baseline.

STATISTICAL ANALYSIS

Continuous within-subject variable data are expressed as mean ±SD. An unpaired t test was used to examine group differences. Two sample Wilcoxon rank sum tests were used to
evaluate between-subject comparisons of primary interest (control vs patient groups). A priori was given to all pairwise differences, and no P value adjustment was made for multiple comparisons. All statistical tests were 2-tailed, and \( P < .05 \) was considered significant for all comparisons. The intraclass correlation coefficient was derived by dividing the standard deviation by the mean, then multiplying by 100.

### RESULTS

#### BASELINE HEMODYNAMIC INDICES

Baseline supine hemodynamic averages are summarized in Table 1. Systolic, diastolic, and mean arterial BPs were significantly higher in the OH group than the control group (\( P < .001 \) for all 3). Systolic BP was also significantly higher in the BOH group than the control group, as was the diastolic BP in the 2_L group (\( P < .05 \) for both). The HR was significantly higher in the OH, BOH, and 2_L groups than in the controls, with the OH group having the highest HR (\( P < .001 \)), followed by the 2_L and BOH groups (\( P < .001 \) for both).

#### DB AND VALSALVA RATIO

The HR response to DB and the Valsalva ratio for the 4 groups are reported in Table 1. The HR response to DB was dramatically impaired in the OH group (\( P < .001 \)), being abnormal (<fifth percentile) in 23 (88%) of the 26 patients. It was also significantly diminished in the BOH group (\( P < .001 \)), being abnormal in 20 (59%) of 34 subjects, and to a lesser degree in the 2_L group (\( P < .001 \)), being abnormal in 15 (62%) of 24 subjects. The Valsalva ratio was reduced for the patient groups compared with the control subjects. However, the difference was not significant (OH group, \( P = .14 \); BOH group, \( P = .58 \); and 2_L group, \( P = .73 \)).

#### MUSCLE SYMPATHETIC NERVE ACTIVITY

To validate the use of reflex vasoconstriction following a decrease in BP (late phase 2 and PRT) as a measure of the adrenergic sympathetic nerve response, we related these indices to directly recorded sympathetic discharges recorded from the peroneal nerve. We analyzed the MSNA response to the VM and its relationship to change in SBP during late phase 2, PRT, and BRS_a. Baseline averages for this group are summarized in Table 2. The mean±SD MSNA response to early phase 2 of the VM was 345.66%±139.85% of baseline MSNA; and during phase 3, 238.84%±228.71% of baseline MSNA. The mean±SD change in SBP during late phase 2 was 28.63±12.70 mm Hg, the PRT was 0.87±0.75 seconds, and the BRS_a was 33.88±24.23 mm Hg/s. There was a strong linear relationship between the MSNA response to early phase 2 and change in SBP during late phase 2. The relationship between MSNA and PRT was strongest for the combined MSNA responses of phases 2 and 3, moderate for the MSNA responses to early phase 2 alone, and weakest between PRT and the MSNA responses to phase 3, indicating that the major driver of PRT is MSNA following early phase 2, supplemented by MSNA following phase 3 (Table 2).

#### ADRENERGIC AND CARDIOVAGAL BRS

The BRS indices were calculated according to the 2 methods explained previously, and are summarized in Table 3. The BRS_a was highest in the healthy control group and was diminished in all 3 patient groups, the decrease being proportional to the severity of adrenergic failure. Compared with controls, the OH group had the largest reduction for BRS_a (\( P < .001 \)), followed by the BOH (\( P < .001 \)) and 2_L (\( P = .009 \)) groups. There was also a gradation in the percentage of patients with reduced values (<fifth percentile) for BRS_a; patients with OH had the largest reduction (23 [88%] of 26 patients), followed by those with BOH (21 [62%] of 34 patients) and then those with 2_L (7 [29%] of 24 patients). Comparisons among patient groups showed significant differences between the 2_L and OH groups (\( P < .001 \)), between the 2_L and BOH groups (\( P = .05 \)), and between the BOH and OH groups (\( P = .001 \)). The PRT correlated with BRS_a for all groups, with the following R values (controls, 0.45; 2_L group, 0.61; BOH group, 0.68; and OH group, 0.75).

The value of 0.75 of phase 3 for BRS_a was chosen because the area under the curve of phase 3 during MSNA was 75% that of early phase 2 MSNA. This formula results in the same pattern of reduction as BRS_a. Compared with controls, the OH group had the largest reduction for BRS_a (\( P < .001 \)), followed by the BOH (\( P < .001 \)) and 2_L (\( P = .003 \)) groups. Comparisons between patient groups showed significant differences between the 2_L and OH groups (\( P = .004 \)), and between the BOH and OH groups (\( P = .04 \)), but no significant difference between the 2_L and BOH groups (\( P = .29 \)). The PRT correlated with BRS_a for all groups, with the following R values (controls, 0.60; 2_L group, 0.38; BOH group, 0.73; and OH group, 0.77).

Figure 1. Example of heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) profiles during the Valsalva maneuver (VM) in a healthy control subject. The part of phase 3 from which adrenergic baroreflex sensitivity and BP recovery time are derived is highlighted. bpm indicates beats per minute; 2_E, early phase 2 of the VM; and 2_L, late phase 2 of the VM.


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CARDIOVAGAL BRS

The BRS_v is defined as the slope of the relationship between SBP and R-R interval during early phase 2 of the VM. The BRS_v was significantly reduced in patients with OH (P < .001) when compared with controls, being abnormal in 10 (71%) of 14 subjects. Again, the BOH (P < .001) and 2_L (P = .003) groups showed less pronounced, but significant, impairment when compared with controls. Values were abnormal in 14 (50%) of the 28 patients with BOH and 10 (53%) of the 19 patients with 2_L. Comparisons between patient groups showed no significant difference between the 2_L and OH groups (P = .28), the BOH and OH groups (P = .21), and the 2_L and BOH groups (P = .87).

GLOBAL BRS

The product of BRS_a and BRS_v was calculated to provide a measure of global baroreflex function (BRS_g). The BRS_g was dramatically reduced in patients with OH (P = .002) and was again impaired, to a lesser but significant degree, in patients with BOH and patients with 2_L (P < .001 for both). Comparisons between patient groups showed no significant differences between the 2_L and OH groups (P = .08), the BOH and OH groups (P = .34), and the 2_L and BOH groups (P = .21).

The main finding of this study is that BRS_a or BRS_v faithfully records the systemic adrenergic sympathetic neural response to changes in BP. The main stimulus for BP decrease is MSNA response to the decrease in BP during early phase 2, supplemented by MSNA response to phase 3 of the VM. In patients with different severities of adrenergic failure, BRS_a provides a more graded response than BRS_v.

The BRS_v is widely used and provides a quantitative index of the chronotropic (vagal) response to alterations in BP. However, the adrenergic (BP) component of the baroreflex is not adequately evaluated. The measurements of orthostatic BP and norepinephrine increment in response to standing up is an important indices.
of adrenergic function but are lacking in sensitivity and specificity. Microneurographic recordings provide a direct recording of sympathetic adrenergic discharges but are invasive and time consuming and require a highly skilled investigator; they, therefore, are not used routinely. Even under optimal conditions, there is a significant failure rate.2 In adrenergic failure, it is difficult, often impossible, to distinguish technical failure from the absence of response.9 The PRT has been a significant advance, quantifying the PRT following the VM. However, to render the index more complete and quantitative, it is necessary to relate PRT to the preceding decrease in BP (which is the stimulus that drives PRT). We originally considered phase 3, because this is the BP deficit immediately preceding BP recovery (PRT) and stimulates MSNA discharge. The PRT composes the time taken to recover from this BP deficit so that BRS_a quantifies a slope function, describing in millimeters of mercury per second the rate of recovery of BP. It composes the adrenergic component of the baroreflex.

Our analysis of microneurographic recordings and BP during the VM is informative. The tight correlation of MSNA resulting from a decrease in BP (early phase 2) followed by baroreflex-mediated vasoconstriction (late phase 2) lends credence to the use of this phase as an index of adrenergic baroreflex response. This index, however, is of limited value quantitatively because the absence of late phase 2 is one of the earliest manifestations of adrenergic failure, occurring even with mild adrenergic failure.50 The advantage of PRT is that it is present in all patients and is proportional to the severity of autonomic failure.4 When PRT was regressed against MSNA, we made the following observations. The PRT correlates best with MSNA from early phase 2 and phase 3 combined, almost as well with MSNA from early phase 2 alone, and at least as well with MSNA from phase 3. Quantitatively, MSNA from early phase 2 composes a larger response than MSNA of phase 3 by 25%. All cases have vigorous early phase 2 MSNA with a variable (sometimes minimal) contribution of phase 3 MSNA. We interpret these findings as follows. Late phase 2 is a baroreflex-mediated vasoconstrictor response to a decrease in BP (early phase 2). When the response is strong and rapid, a prominent late phase 2 is seen and the PRT is brief. In adrenergic failure, the response is slowed and, hence, late phase 2 is absent (because PRT is delayed) and the delayed and reduced vasoconstrictor response is manifest as increased PRT. Indeed, PRT is the continuation of late phase 2 interrupted by phase 3.

The BRS_a or BRS_a1 is significantly reduced in all groups of patients with minor to severe adrenergic failure.4

### Table 3. Summary Statistics for BRS_v, BRS_a, and BRS_g

<table>
<thead>
<tr>
<th>Variable</th>
<th>OH Group</th>
<th>BOH Group</th>
<th>2_L Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRS_v</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of individuals</td>
<td>14</td>
<td>28</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Median (IQR), ms/mm Hg</td>
<td>1.34 (2.07)</td>
<td>2.02 (2.53)</td>
<td>1.81 (2.53)</td>
<td>4.83 (2.64)</td>
</tr>
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<td>Range, ms/mm Hg</td>
<td>0.20-8.44</td>
<td>0.69-9.15</td>
<td>0.33-10.39</td>
<td>1.24-13.09</td>
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<tr>
<td>BRS_a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of individuals</td>
<td>26</td>
<td>34</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Median (IQR), mm Hg/s</td>
<td>4.78 (6.32)</td>
<td>9.66 (10.14)</td>
<td>15.69 (10.84)</td>
<td>24.54 (19.33)</td>
</tr>
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<td>Range, mm Hg/s</td>
<td>0.93-18.31</td>
<td>1.50-31.29</td>
<td>1.68-50.00</td>
<td>10.22-55.33</td>
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<td>BRS_g</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of individuals</td>
<td>11</td>
<td>17</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Median (IQR), mm Hg</td>
<td>4.73 (6.66)</td>
<td>11.17 (14.90)</td>
<td>17.07 (18.74)</td>
<td>28.12 (17.77)</td>
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<td>Range, mm Hg</td>
<td>0.91-18.17</td>
<td>1.39-30.24</td>
<td>1.76-56.94</td>
<td>12.98-70.65</td>
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<td>BRS_g1</td>
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<tr>
<td>No. of individuals</td>
<td>14</td>
<td>28</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>Median (IQR), ms/s</td>
<td>7.16 (19.75)</td>
<td>20.23 (23.12)</td>
<td>32.61 (64.74)</td>
<td>98.51 (65.53)</td>
</tr>
<tr>
<td>Range, ms/s</td>
<td>0.53-30.21</td>
<td>1.31-253.82</td>
<td>2.50-208.48</td>
<td>28.55-294.53</td>
</tr>
<tr>
<td>BRS_v</td>
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<td></td>
<td></td>
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<tr>
<td>No. of individuals</td>
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<td>15</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Median (IQR), ms</td>
<td>15.37 (21.59)</td>
<td>23.48 (41.54)</td>
<td>35.25 (58.80)</td>
<td>128.55 (110.68)</td>
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<tr>
<td>Range, ms/s</td>
<td>1.06-29.98</td>
<td>1.88-269.78</td>
<td>3.18-187.63</td>
<td>37.17-350.08</td>
</tr>
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</table>

Abbreviations: BOH, borderline orthostatic hypotension; BRS_a, adrenergic baroreflex sensitivity; BRS_a1, alternative BRS_a; BRS_g, global BRS; BRS_g1, alternative BRS_g; BRS_v, vagal BRS; IQR, interquartile range; OH, orthostatic hypotension; 2_L, patients with loss of late phase 2 of the Valsalva maneuver.
ure. More important, it provides information on a different (adrenergic) component of the baroreflex. The pattern of response for these groups is different for BRS_a (or BRS_a) and BRS_v. While BRS_v and BRS_a (or BRS_a) are reduced for all groups of patients with adrenergic failure, the changes in BRS_a (or BRS_a) are more graded, increasing with greater severity and distribution of adrenergic failure. This difference, which has been previously noted, likely reflects the more diffuse nature of arterioles whose vasoconstrictor response results in PRT.

Each of the 3 indices (PRT, BRS_a, and BRS_a) has its advantages and disadvantages. Both BRS_a and BRS_a are reasonable indices of adrenergic BRS. We chose BP at the trough of phase 3 as the numerator in calculating BRS_a because this BP change immediately precedes PRT and reflects in part early phase 2 in patients with autonomic failure. An alternative formula (BRS_a), with microneurographic support, would substitute combined BP deficits (early phase 2 and additional BP change in phase 3). For this equation, the numerator is early phase 2 plus 0.75 of phase 3. The BRS_a has greater support from microneurographic validation. However, many patients have minimal early phase 2 (hence, a smaller number for BRS_a than BRS_a). Hence, we have chosen to retain both indices.

How does PRT compare with BRS_a (or BRS_a)? The PRT is always available and is easy to quantify. The criticism is that it lacks a numerator, composing the stimulus that drives BP recovery. However, PRT regresses significantly with BRS_a and BRS_a and especially well with patients with autonomic failure, so that patients with OH have R values of 0.75 for BRS_a and 0.77 for BRS_a. The PRT remains a useful index and may be the only available index in those patients in whom BRS_a cannot be calculated. When the reproducibility of PRT with BRS was compared, PRT and BRS_a (or BRS_a) are highly reproducible, but when the same subject performs multiple VMs, resulting in different BP alterations, BRS_a (or BRS_a) is consistently superior to PRT because it corrects for the change in BP. Our conclusion is that BRS_a (or BRS_a) is preferable, but PRT provides an approximation and is valuable in situations in which adrenergic BRS cannot be derived.

The formulation of BRS_v and BRS_a is different and warrants comment. The heart period response to BP change is clearly time locked to beat-to-beat BP so that BRS_v is defined by a linear regression. In contrast, the temporal relationship between the stimulus (BP decrease) and response (BP recovery) is delayed by a variable duration, reflecting the slow vasoconstrictor behavior of smooth muscle. It is not possible to reliably regress the 2 curves. We chose instead to express the 2 as a ratio. It does have the limitation that the recovery time likely reflects a combination of baroreflex-mediated vasoconstriction and elastic recoil, and other factors.

In conclusion, the approach in this study results in a more comprehensive evaluation of autonomic failure. We can separately quantify the vagal component of the baroreflex (BRS_v), the adrenergic component (BRS_a or BRS_a), or combine both limbs of the baroreflex in BRS_g or BRS_g. It is important information to the managing neurologist to know whether the vagal or adrenergic components of the baroreflex are affected. The clinical autonomic laboratory is in a position to measure these components. These values are likely to be important in the diagnosis of early autonomic failure and in monitoring the progression of disease and the response to treatment.

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