

## Autonomic Reflex Dysfunction in Patients Presenting for Elective Surgery Is Associated with Hypotension after Anesthesia Induction

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**Background:** Autonomic reflex dysfunction in patients with diabetes is associated with an increased incidence of hypotension after induction of anesthesia. Whether this finding can be extrapolated to patients with autonomic dysfunction from other causes (e.g., advanced age, hypertension, altered ventricular function) has not been established.

**Methods:** The authors investigated whether autonomic reflex dysfunction in a more generalized patient group (26 consecutively consenting day-surgery patients older than 39 yr) was similarly associated with the occurrence of hypotension after induction. Preoperative tests of autonomic function included: Valsalva maneuver, change in heart rate with forced breathing, change in heart rate and blood pressure with standing, and spectral analysis of heart rate variability. Anesthesia was induced with 3–5 mg/kg thiopental, 2 µg/kg fentanyl, and 60% N<sub>2</sub>O; 0.1 mg/kg vecuronium was used for paralysis; 0–1.5% isoflurane was added for maintenance of anesthesia after intubation. Noninvasive measurements of mean blood pressure were obtained every minute for 10 min after induction and then every 3 min until skin incision.

**Results:** Twelve patients developed hypotension (mean blood pressure < 70 mmHg), and 14 patients did not. Measurements of autonomic reflex function were significantly more abnormal in the patients who developed hypotension ( $P < 0.006$  for Valsalva measurements, heart rate variability parameters, and change in heart rate with forced breathing). Using critical test values for autonomic tests, the incidence of hypotension

was 67–83% in patients with autonomic nervous system dysfunction versus 9–17% in other patients.

**Conclusions:** The results document that: (1) some degree of autonomic reflex dysfunction is not uncommon in patients older than 39 yr presenting for elective surgery, and (2) such dysfunction is associated with an increased incidence of hypotension when using the described induction technique. (Key words: Autonomic nervous system, dysfunction: heart rate variability; Valsalva maneuver.)

BURGOS *et al.* have previously demonstrated an increased incidence of hypotension after anesthesia induction in patients with diabetes with autonomic neuropathy.<sup>1</sup> Although autonomic nervous system (ANS) reflex dysfunction is a well recognized complication of diabetes, varying degrees of ANS dysfunction also accompany multiple other medical conditions. Alterations in ANS reflex function have been documented in patients with advanced age,<sup>2,3</sup> hypertension,<sup>4–6</sup> altered ventricular function,<sup>7–10</sup> myocardial infarction,<sup>11,12</sup> coronary artery disease,<sup>13,14</sup> and various drug therapies (e.g., β-adrenergic blockers,<sup>15,16</sup> calcium channel blockers,<sup>17,18</sup> angiotensin-converting enzyme inhibitors,<sup>19,20</sup> central α-adrenergic agents<sup>21,22</sup>). We hypothesized that patients with ANS dysfunction from any cause (diabetes or other medical conditions) would be at increased risk for hypotension after anesthesia induction.

We investigated this hypothesis in patients older than 39 yr presenting for elective surgery and admitted to our day-surgery units. ANS reflex dysfunction was evaluated using: (1) standard tests of autonomic function (Valsalva maneuver, change in heart rate with vital capacity breathing, change in heart rate and blood pressure upon assuming upright posture), and (2) power spectral analysis of heart rate variability (HRV). HRV refers to small, spontaneous oscillations in heart rate associated with the activity of homeostatic ANS reflexes.<sup>16,23–28</sup> Power spectral analysis of HRV allows precise measurements of the power (equal to statistical variance) of heart rate oscillations occurring in specific

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## REFLEX DYSFUNCTION AND HYPOTENSION

frequency bands (similar to spectral analysis of the electroencephalogram waveform). Recent studies demonstrated that measurements of high frequency (above 0.15 Hz) and low frequency (below 0.15 Hz) HRV power provide information about the integrity and activity of parasympathetic and sympathetic reflexes, respectively.<sup>16,25,26</sup> Some investigators have subdivided low-frequency HRV into smaller frequency bands, the most common of which is mid-frequency HRV (typically from 0.05–0.07 Hz to 0.12–0.15 Hz). Mid-frequency HRV is centered about the reported frequency of steady-state baroreceptor modulation of heart rate (0.1 Hz), and may be less influenced by more slowly adapting neurohumoral reflexes that are thought to affect very low-frequency HRV (below 0.03–0.04 Hz).<sup>23,28,29</sup> ANS reflex dysfunction is characterized by decreases in one or more components of HRV and/or a lack of change in HRV during defined experimental interventions.<sup>3,6,9,12,25,30</sup>

Our results document that some degree of ANS dysfunction is not uncommon in patients older than 39 yr presenting for elective surgery and that such dysfunction is associated with an increased incidence of hypotension after anesthesia induction.

## Methods

After receiving approval from our Institutional Review Board, we evaluated 26 consecutively consenting day-surgery patients. Patients ranged in age from 40 to 75 yr ( $52 \pm 2.0$ ). Nineteen patients were women, and seven were men. Patients were not included or excluded from the study on the basis of any specific medical conditions. Concomitant medical conditions included: hypertension ( $n = 10$ ), diabetes mellitus ( $n = 4$ ), known coronary artery disease ( $n = 2$ ), and advanced age (age  $> 60$  yr,  $n = 7$ ). Four patients were receiving  $\beta$  blockers, three were receiving calcium channel blockers, and three were receiving angiotensin-converting enzyme inhibitor therapy. Preoperative administration of medications was not altered for purposes of this study but was determined by the patients' attending physicians. Because testing of autonomic function was carried out in the immediate preoperative period, the effects of such medications on ANS reflex function should have been similar during both the testing period and induction of anesthesia.

### Standard Autonomic Tests

Tests of autonomic function were performed before administration of any sedative medications. For these

tests, continuous digital recordings of the electrocardiogram (sampling rate 250 Hz) were collected using an Intel-80386-based computer with a Metrabyte analog-to-digital conversion board. Tests performed upon patients in the supine position were: (1) change in heart rate with forced-breathing, (2) Valsalva maneuver, and (3) resting HRV. For the forced breathing test, patients were instructed to perform six vital capacity breaths during a 60-s period, with each inspiration and each expiration lasting approximately 5 s.<sup>1,31</sup> The change in heart rate was calculated as the difference between the average maximum heart rate (determined from a computerized display of beat-to-beat heart rate) and the average minimum heart rate over all six breaths. For the Valsalva maneuver, patients were instructed to exhale into a mouthpiece (beginning at normal end-inspiration) and maintain 40 mmHg of positive pressure for 15 s.<sup>1,32,33</sup> After release of the positive pressure, patients were instructed to breathe quietly for 1 min. The control heart rate, phase III heart rate (fastest heart rate occurring immediately after release of positive pressure), and phase IV heart rate (slowest heart rate within 30 s after release of positive pressure) were derived from a computerized display of beat-to-beat heart rate (in beats/minute). Standard Valsalva measurements based on changes in RR intervals were calculated by converting heart rate in beats/minute to RR intervals in milliseconds using the relationship  $RR \text{ interval} = 60,000/\text{heart rate}$ . These standard Valsalva measurements included: (1) strain response, control RR interval minus phase III RR interval; (2) Valsalva ratio, phase IV RR interval divided by phase III RR interval; and (3) Valsalva index, phase IV RR interval minus phase III RR interval.<sup>1,32</sup> For the purpose of comparisons with HRV measurements, which were calculated based on variations in heart rate rather than variations in RR intervals, we also calculated the following modified Valsalva measurements based on changes in heart rate: (1) modified strain response, peak heart rate in phase III minus control heart rate; and (2) modified Valsalva index, peak heart rate in phase III minus minimum heart rate in phase IV.

After completing the Valsalva maneuver and forced breathing test, the patients were instructed to lie quietly for 10 min. During this interval, data were collected for measurements of resting heart rate, resting blood pressure, and resting HRV. Resting blood pressure was calculated as the average of three automated oscillometric measurements (Nellcor N-CAT) taken over this 10-min period. The patient then was in-

structed to stand erect beside the bed. Three additional noninvasive measurements of blood pressure at 2-min intervals were taken beginning 30 s after assumption of the upright position. The changes in diastolic blood pressure and mean blood pressure with standing were calculated as the change in the average of the three measurements taken in the supine and standing positions. The change in heart rate with standing was calculated as the difference in average heart rate between these same time periods.

#### *Power Spectral Analysis of HRV*

The methods used to derive HRV power spectral measurements have been described in detail elsewhere.<sup>34</sup> Using a cross-correlation technique, each QRS complex in the digitally recorded electrocardiogram signal was identified, and a beat-to-beat heart rate signal (effective sampling rate of 4 Hz) was constructed. This heart rate signal was prefiltered to remove signal components at frequencies outside the range of interest (less than 0.03 Hz and greater than 0.5 Hz). This filtered heart rate signal was divided into overlapping 64-s segments, with successive segments beginning every 15 s. Power spectral analysis of each 64-s segment was performed using the fast Fourier transform (windowed periodogram technique).<sup>34,35</sup> The sequential HRV power spectra (plotted as a three-dimensional surface) from one of the study subjects are shown in figure 1. For each spectra, the HRV power in specific frequency ranges was calculated by integration of the area under the curve between the defined frequency limits (similar to calculation of power in specific frequency bands of the electroencephalogram). Specific HRV parameters calculated in the present study were: (1) mid-frequency HRV power (HRVmid), power between 0.07 and 0.15 Hz; (2) high-frequency HRV power (HRVhi), power between 0.15 and 0.3 Hz; and (3) total HRV power (HRVtot), power between 0.03 and 0.3 Hz. Trended measurements of HRVmid and HRVhi also are shown in figure 1. The frequency bands used for these parameters are based on the frequency location of characteristic peaks in the HRV power spectrum associated with the activity of different reflexes. The high-frequency band corresponds to the expected frequency of the respiratory sinus arrhythmia (*i.e.*, the frequency of respiration), and the mid-frequency band is centered about the reported frequency (0.1 Hz) of the HRV peak attributed to steady-state baroreceptor modulation of heart rate.<sup>28,29</sup>

We analyzed HRV using units of both power and standard deviation. HRV power in (beats/minute)<sup>2</sup> represents a frequency-specific measure of the variance<sup>36</sup> in the beat-to-beat heart rate signal and is related to the square of the amplitude of heart rate oscillations. The square root of HRV power represents a frequency-specific measure of the standard deviation<sup>36</sup> in the beat-to-beat heart rate signal and is more proportional to the amplitude (*vs.* the square of the amplitude) of heart rate oscillations. HRV standard deviation has units of beats/minute, which are more similar to the units used for other heart rate-based tests of ANS dysfunction. In the current study, measurements expressed in units of standard deviation are denoted by "SD" preceding the "HRV" (SDHRVmid, SDHRVhi, SDHRVtot). Standard deviation measurements were obtained by taking the square root of the corresponding HRV power measurement (*e.g.*, for a given HRV spectra, SDHRVmid is equal to the square root of HRVmid).

The median values of trended HRV parameters (fig. 1) obtained during the period of supine rest were calculated for each patient. These median values were correlated with other autonomic test results using linear regression. Median values were used in preference to average values because median values are a more resistant statistic for measurement of central tendency when the data sets may include infrequent extreme measurements.<sup>37</sup> An additional desirable property of the median is that it is not influenced by the conversion between units of HRV power and HRV standard deviation (*e.g.*, for a defined set of HRV spectra, the median value of SDHRVmid is equal to the square root of the median value of HRVmid; in contrast, the average value of SDHRVmid is not equal to the square root of the average value of HRVmid). These median values for each patient also were used for comparisons between patient groups as described below.

#### *Anesthetic Management*

The primary anesthesiologist responsible for patient management was unaware of the preoperative test results. Patients were not premedicated before induction of anesthesia. After preoxygenation, anesthesia induction was carried out using 2  $\mu$ g/kg fentanyl, 3–5 mg/kg thiopental, and 60% N<sub>2</sub>O in O<sub>2</sub>. After loss of consciousness, 0.1 mg/kg vecuronium was administered for muscle relaxation. The trachea was intubated approximately 3 min after vecuronium administration. After intubation, isoflurane (up to a maximum concentration of 1.5%) was added to the 60% N<sub>2</sub>O for mainte-

## REFLEX DYSFUNCTION AND HYPOTENSION

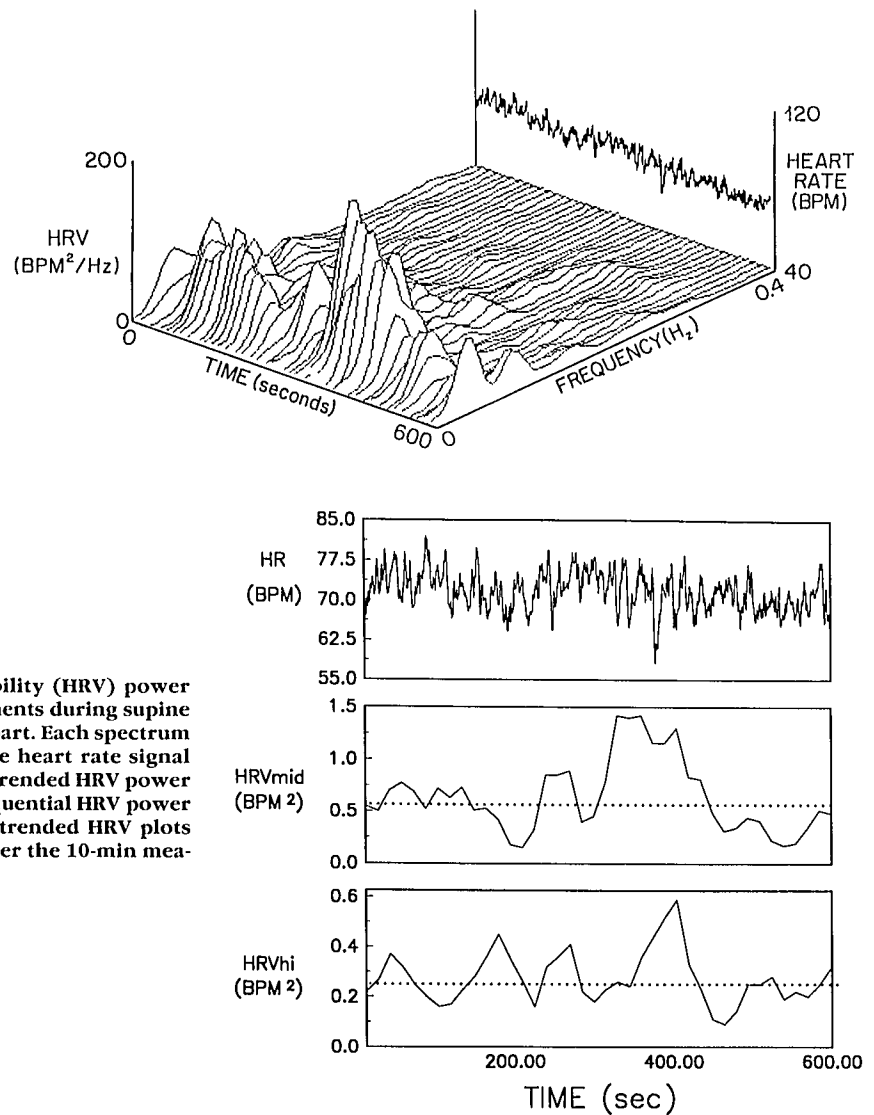


Fig. 1. Heart rate signal, heart rate variability (HRV) power spectra, and trended HRV power measurements during supine rest. Power spectra (*top*) are spaced 15 s apart. Each spectrum was derived from a 64-s data epoch of the heart rate signal (32 s on each side of the plotted spectra). Trended HRV power measurements were derived from these sequential HRV power spectra (*bottom*). The dotted lines in the trended HRV plots depict the median values of HRV power over the 10-min measurement period.

nance of anesthesia. The primary anesthesiologist was allowed to adjust the isoflurane dose as clinically indicated and to discontinue the isoflurane in hemodynamically unstable patients. Automated noninvasive blood pressure measurements were recorded every minute beginning in the preinduction period until 10 min after intubation, and then every 3 min until 10 min after incision.

#### Data Analysis

Pearson's product moment correlation was used to test correlations between standard tests of autonomic function and HRV measurements. To evaluate the as-

sociation between ANS dysfunction and hypotension, patients were divided into two groups based on the occurrence of hypotension (mean blood pressure less than 70 mmHg) after induction (group H hypotension; group N no hypotension). Statistical significance of differences between groups H and N for the incidence of specific medical conditions, autonomic test results, anesthetic dose, and fluid administration were assessed using Fisher's exact test for binomial data and the unpaired *t* test for continuous data. Similar to the method used by Burgos,<sup>1</sup> we identified critical test values for those autonomic tests that were most significantly different between groups; critical test values were iden-

tified that resulted in optimal sensitivity and specificity for retrospective identification of patients who developed hypotension. Fisher's exact test was used to compare the incidence of hypotension in patients with positive *versus* negative tests. For all statistical comparisons, *P* values less than 0.05 were considered significant.

## Results

### Correlation between Autonomic Tests

Highly significant correlations were observed between HRV parameters and other heart rate-based autonomic tests (figs. 2 and 3, table 1). Correlations with Valsalva measurements were greater when test results were calculated using changes in heart rate (modified Valsalva parameters calculated in beats/minute) rather than changes in RR intervals (in milliseconds; fig. 2). Correlations were also greater when HRV parameters were expressed in beats/minute (*i.e.*, SDHRV<sub>mid</sub>, SDHRV<sub>hi</sub>, SDHRV<sub>tot</sub>) rather than (beats/minute)<sup>2</sup> (*i.e.*, HRV<sub>mid</sub>, HRV<sub>hi</sub>, HRV<sub>tot</sub>; fig. 3). For both the modified Valsalva index and the modified strain index, correlations with all SDHRV parameters had *r* values greater than or equal to 0.77. The Valsalva ratio was highly correlated with SDHRV<sub>hi</sub> (*r* = 0.81), but less well correlated with SDHRV<sub>mid</sub> (*r* = 0.68) and SDHRV<sub>tot</sub> (*r* = 0.61). Correlation coefficients between the change in heart rate with forced breathing and SDHRV parameters ranged between 0.70 and 0.76; the highest correlation was between change in heart rate and SDHRV<sub>hi</sub> (fig. 3). Examination of these latter data (fig. 3) suggests a possible plateau in this relationship for values of

SDHRV<sub>hi</sub> exceeding 0.6 beats/min. If the four patients with SDHRV<sub>hi</sub> values above 0.6 are excluded, the correlation coefficient increases to 0.91.

### Clinical Outcome and Autonomic Test Results

Twelve patients developed hypotension (group H), and 14 patients did not (group N). As shown in table 2, there were no significant differences between groups for the incidence of specific medical conditions (diabetes, hypertension, known coronary artery disease, advanced age, or use of specific medications), anesthetic doses, or fluid administration. Patients in group H ranged in age from 43 to 75 yr. The average age of patients in group H was older than the average age in group N ( $57 \pm 3.1$  *versus*  $48 \pm 2.2$ ; *P* = 0.025).

There was no significant difference between groups for baseline mean blood pressure (obtained during the 10-min period of supine rest; group H  $96 \pm 4$ , group N  $100 \pm 2$  mmHg) or immediate preinduction mean blood pressure (group H  $115 \pm 6$ , group N  $117 \pm 4$  mmHg). Significant group differences in mean blood pressure occurred at minutes 4, 5, 16, and 19; there were no significant group differences in mean heart rate (fig. 4). The maximum percent decrease in blood pressure was significantly greater for patients in group H compared to patients in group N when expressed as a percent change from either baseline ( $-35 \pm 2\%$  *vs.*  $-19 \pm 3\%$ , *P* < 0.001) or preinduction values ( $-45 \pm 2\%$  *vs.*  $-29 \pm 3\%$ , *P* < 0.001).

There were highly significant differences between groups for most autonomic tests (figs. 5–8). *P* values were less than or equal to 0.006 for the change in heart rate with forced breathing, for all Valsalva parameters, and for all SDHRV parameters. For HRV parameters, the

**Table 1. Correlations between Autonomic Tests**

Test	HRV <sub>mid</sub>	HRV <sub>hi</sub>	HRV <sub>tot</sub>	SDHRV <sub>mid</sub>	SDHRV <sub>hi</sub>	SDHRV <sub>tot</sub>
Valsalva index (ms)	0.46 (0.020)	0.68 (0.001)	0.57 (0.002)	0.57 (0.002)	0.76 (0.001)	0.68 (0.001)
Modified valsalva index (beats/min)	0.63 (0.001)	0.74 (0.001)	0.67 (0.000)	0.78 (0.001)	0.79 (0.001)	0.77 (0.001)
Strain index (ms)	0.47 (0.015)	0.67 (0.001)	0.46 (0.018)	0.59 (0.002)	0.75 (0.001)	0.58 (0.002)
Modified strain index (beats/min)	0.66 (0.000)	0.74 (0.001)	0.70 (0.001)	0.78 (0.001)	0.79 (0.001)	0.79 (0.001)
Valsalva ratio	0.58 (0.002)	0.75 (0.001)	0.50 (0.010)	0.68 (0.001)	0.81 (0.001)	0.61 (0.001)
ΔHR forced breathing (beats/min)	0.51 (0.008)	0.62 (0.001)	0.55 (0.004)	0.70 (0.001)	0.76 (0.001)	0.71 (0.001)
ΔHR standing (beats/min)	0.42 (0.032)	0.50 (0.010)	0.45 (0.022)	0.49 (0.010)	0.48 (0.010)	0.49 (0.012)
HRV <sub>mid</sub> , SDHRV <sub>mid</sub> ((beats/min) <sup>2</sup> )	1.00 (0.001)	0.83 (0.001)	0.99 (0.001)	1.00 (0.001)	0.86 (0.001)	0.99 (0.001)
HRV <sub>hi</sub> , SDHRV <sub>hi</sub> ((beats/min) <sup>2</sup> )	0.83 (0.001)	1.00 (0.001)	0.88 (0.001)	0.86 (0.001)	1.00 (0.001)	0.91 (0.001)

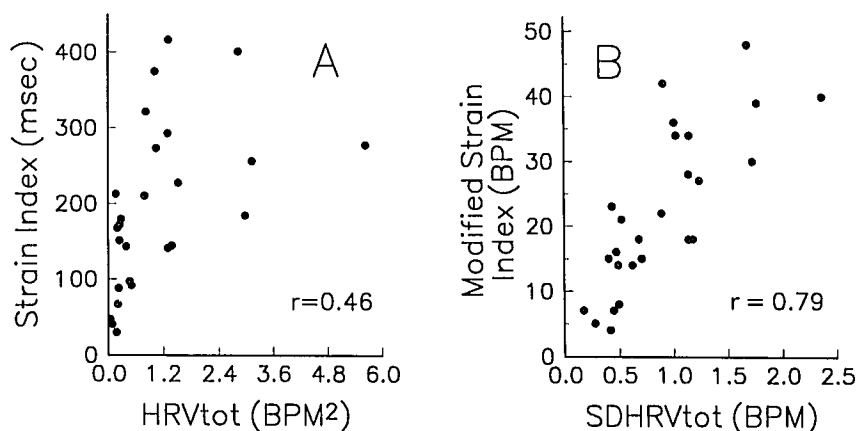
Values depicted are Pearson's product moment correlation with the corresponding *P* values in parentheses.

HRV frequency bands: mid = 0.07–0.15 Hz; hi = 0.15–0.30 Hz; tot = 0.03–0.30.

ΔHR = change in heart rate; HRV = heart rate variability power in (beats/minute)<sup>2</sup>; SDHRV = heart rate variability standard deviation in beats/minute (see text).

## REFLEX DYSFUNCTION AND HYPOTENSION

Fig. 2. (A) Correlation between values of total heart rate variability power (HRVtot) and values of the strain index. (B) Correlation between values of total heart rate variability standard deviation (SDHRVtot) and values of the modified strain index. Note the improved correlation (B) when test results are expressed in the same units of measurement (beats/minute).



significance of group differences was consistently higher when HRV parameters were expressed in units of standard deviation rather than units of power (figs. 7 and 8). The changes in blood pressure with standing were statistically significant between groups, but much

less so than other autonomic tests (diastolic blood pressure  $1 \pm 3$  mmHg group H vs.  $7 \pm 2$  mmHg group N,  $P = 0.036$ ; mean blood pressure  $1 \pm 3$  mmHg group H vs.  $8 \pm 2$  mmHg group N,  $P = 0.042$ ). The change in heart rate with standing was not significantly different between groups.

Plots of specific test values for the patients in each group confirmed that the incidence of hypotension increased with test values indicative of more ANS dysfunction (figs. 5–8). Selected critical test values for each autonomic test are depicted by the dotted lines

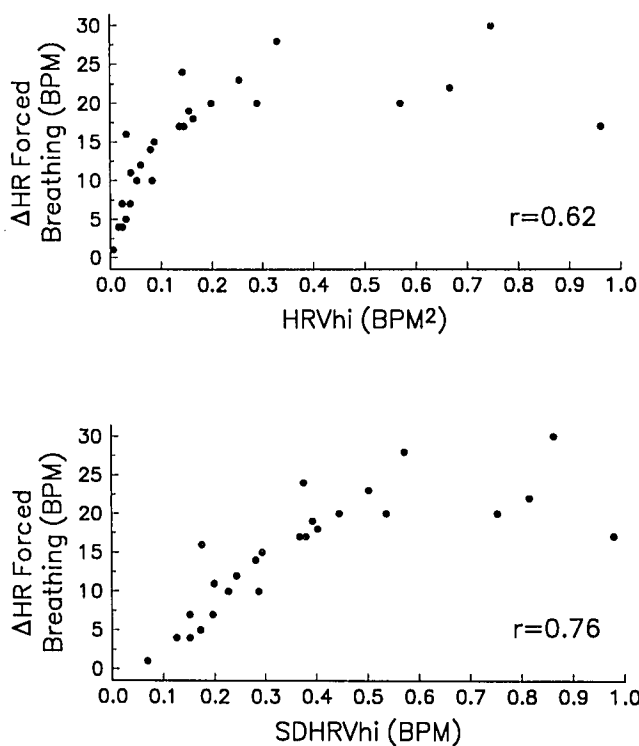


Fig. 3. Correlations between values of high-frequency HRV power (HRVhi), high-frequency HRV standard deviation (SDHRVhi), and the change in heart rate during forced breathing.

Table 2. Group Comparisons

Variable	Group H (n = 12)	Group N (n = 14)	P
Hypertension	6	4	NS*
Diabetes mellitus	2	2	NS*
Age >60 yr	5	2	NS*
Coronary artery disease	2	0	NS*
Heart failure	0	0	NS*
β blocker therapy	2	2	NS*
Calcium channel blocker therapy	2	1	NS*
Ace inhibitor therapy	1	2	NS*
Male	4	3	NS*
End-tidal isoflurane (%)†	0.40 (0.07)	0.55 (0.10)	NS‡
Thiopental dose (mg/kg)	4.06 (0.10)	4.23 (0.14)	NS‡
Pre-induction fluid (ml/kg)	2.75 (0.41)	2.99 (0.44)	NS‡
Pre-incision fluid (ml/kg)	5.82 (0.49)	6.47 (0.73)	NS‡

Values in parenthesis are SEM.

\* Significance by Fisher's exact test.

† Isoflurane concentration recorded at time of minimum blood pressure. Inspired concentration was substituted for end-tidal concentration in two patients in group H and three patients in group N for whom end-tidal concentrations were unavailable.

‡ Significance by unpaired *t* test.

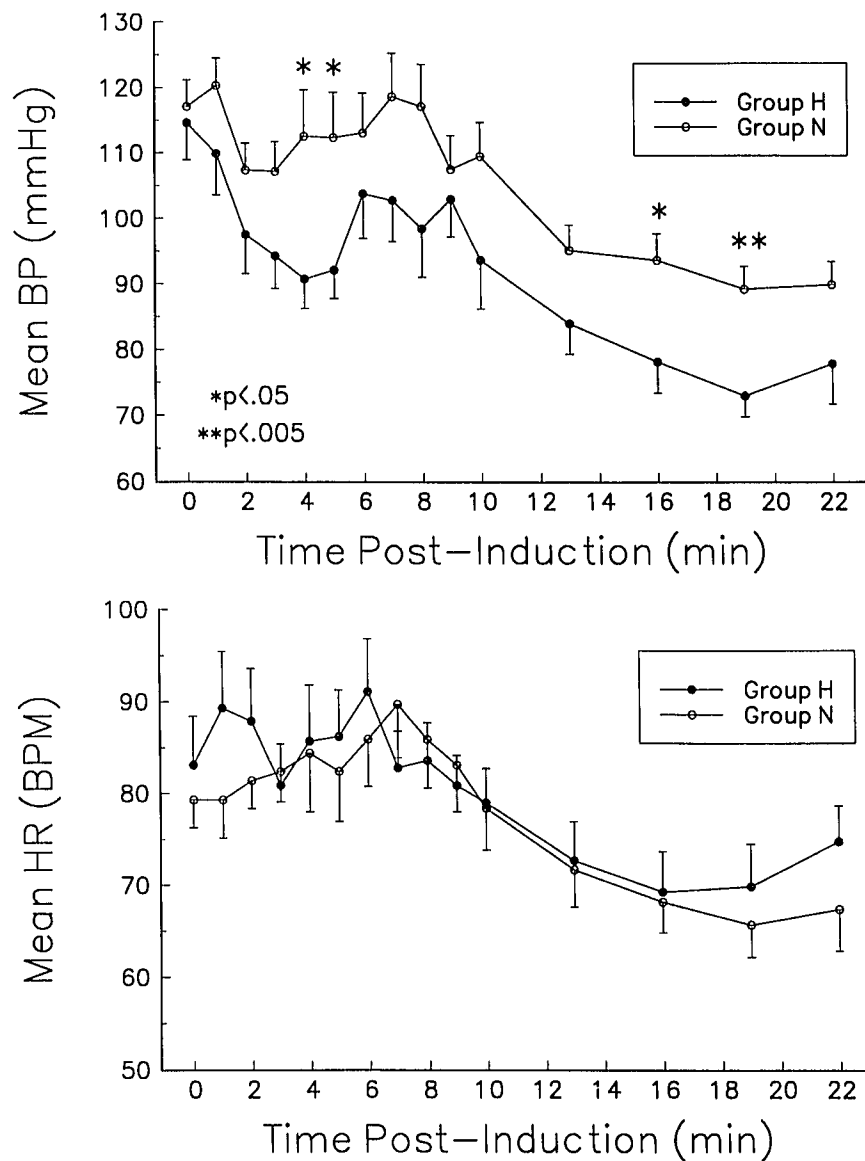


Fig. 4. Group mean blood pressure and heart rate values (error bars depict SEM) during the first 22 min after induction. Values recorded after surgical incision (two patients in each group for the data shown) were excluded. Statistical significance by unpaired *t* test.

in each figure and are tabulated in table 3. The incidence of hypotension in patients with positive and negative tests, as well as calculations of test sensitivity and specificity, are listed in table 3. The incidence of hypotension was 67–83% in patients with positive tests versus 9–17% in patients with negative tests.

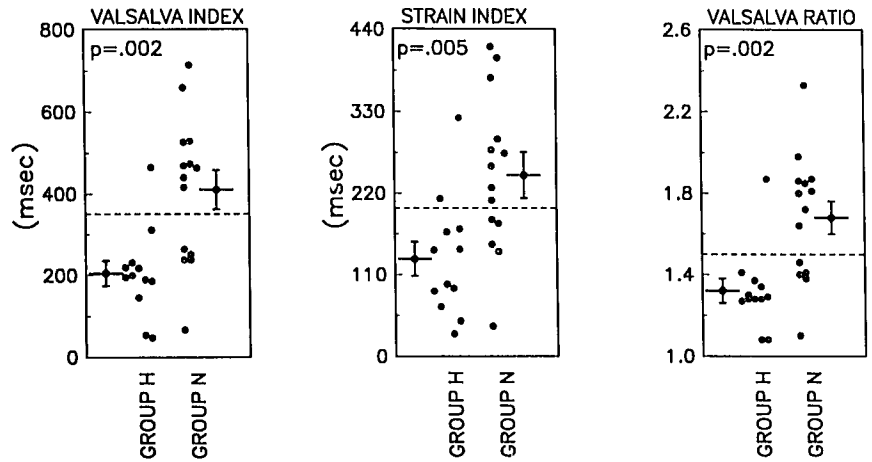
**Discussion**

Our results document that preexisting ANS reflex dysfunction, as measured by several autonomic tests,

is associated with a higher incidence of postinduction hypotension. These results are similar to those reported previously by Burgos in patients with diabetes.<sup>1</sup> Our results extend these observations to patients with ANS dysfunction from other causes. Other known etiologies of ANS dysfunction include advanced age,<sup>2,3</sup> hypertension,<sup>4-6</sup> altered ventricular function,<sup>7-10</sup> myocardial infarction,<sup>11,12</sup> coronary artery disease,<sup>13,14</sup> and various drug therapies.<sup>16-22</sup> Our results document that significant ANS reflex dysfunction (of sufficient degree to be associated with a higher incidence of postinduction hypotension) is

REFLEX DYSFUNCTION AND HYPOTENSION

Fig. 5. Autonomic test results for patients in groups H and N. The mean  $\pm$  SEM for each group is depicted by the horizontal line with error bars. The dashed line indicates the critical test value used for each test (table 3).



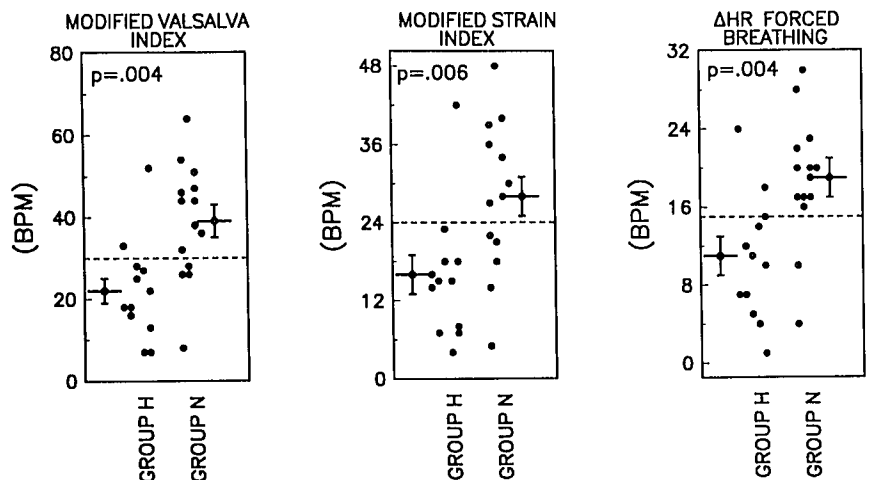
not uncommon in patients older than 39 yr presenting for elective surgery.

Our results suggest that preoperative ANS reflex dysfunction may be a significant factor in the hemodynamic response to anesthetic induction. There are several mechanisms by which ANS dysfunction might influence this hemodynamic response. One probable mechanism is that homeostatic reflexes in patients with ANS dysfunction are less able to compensate for the effects of anesthetic induction on venous return, vascular tone, and myocardial contractility. Alternatively, patients with ANS reflex dysfunction may be less able to tolerate further depression of homeostatic reflexes by the administered anesthetics. A third possible mechanism is that preexisting alterations in ANS function may influence the indirect effects of anesthetics on vascular and

myocardial function (*i.e.*, those effects mediated by anesthetic-induced alterations in autonomic tone).<sup>27</sup> The relative contribution of these possible mechanisms to the increased incidence of hypotension that we observed in patients with ANS dysfunction cannot be determined from the present study. Although we hypothesize that the increased incidence of hypotension is causally related to ANS dysfunction, an alternative hypothesis is that ANS reflex dysfunction is simply a marker for patients with some other concomitant condition that is the more proximate cause for hypotension.

In our small group of study patients, hypotension was more strongly associated with the presence of ANS dysfunction than with the presence of any specific medical condition (table 2). Although these listed medical conditions are associated with the occurrence of ANS

Fig. 6. Autonomic test results for patients in groups H and N. The mean  $\pm$  SEM for each group is depicted by the horizontal line with error bars. The dashed line indicates the critical test value used for each test (table 3).





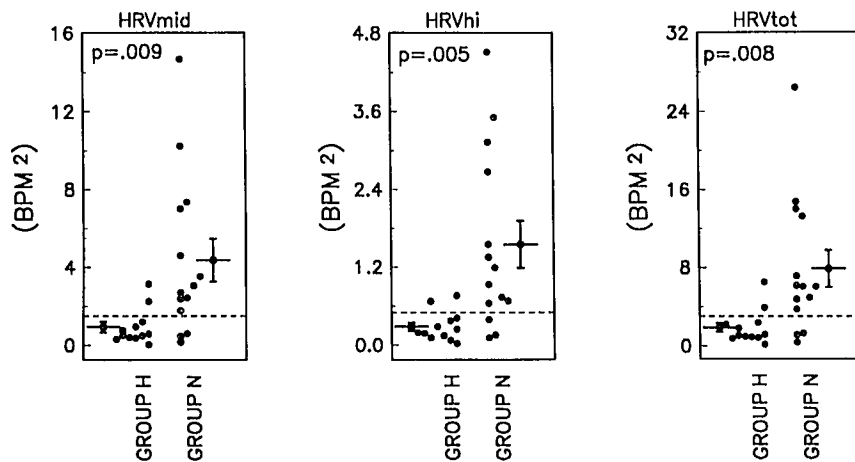


Fig. 7. Autonomic test results for patients in groups H and N. The mean  $\pm$  SEM for each group is depicted by the horizontal line with error bars. The dashed line indicates the critical test value used for each test (table 3).

reflex dysfunction, the degree of reflex dysfunction is variable among patients. Our inability to demonstrate a relationship between these medical conditions and the occurrence of hypotension was limited by the low incidence of each condition in this unselected study group (*i.e.*, patients were not included or excluded on the basis of defined medical conditions). However, because multiple medical conditions are associated with ANS reflex dysfunction, the incidence of ANS dysfunction in this study group was sufficiently common that a significant relationship between ANS dysfunction and hypotension could be identified.

The mean age of patients who became hypotensive ( $57 \pm 3.1$ ) was higher than the mean age of other patients ( $48 \pm 2.2$ ). This is an expected finding because of both the increased incidence of concomitant medical conditions with advanced age, as well as a possible

independent effect of advanced age on reflex function.<sup>2,3</sup> However, the age range of patients who became hypotensive (43–75 yr) was similar to that of other patients (40–66 yr), such that the significance of this age difference between groups was limited ( $P = 0.025$ ) in comparison to group differences for most autonomic tests (figs. 5–8).

Both power spectral measurements of HRV and other autonomic tests are believed to have some specificity for analysis of sympathetic *versus* parasympathetic reflex function. Tests used in the current study that are believed to be more specific for sympathetic function include the strain index, the change in heart rate and blood pressure with standing, and the mid-frequency HRV parameters.<sup>1,25</sup> Tests that are thought to be more specific for parasympathetic function include the Valsalva ratio, the Valsalva index, change in RR interval

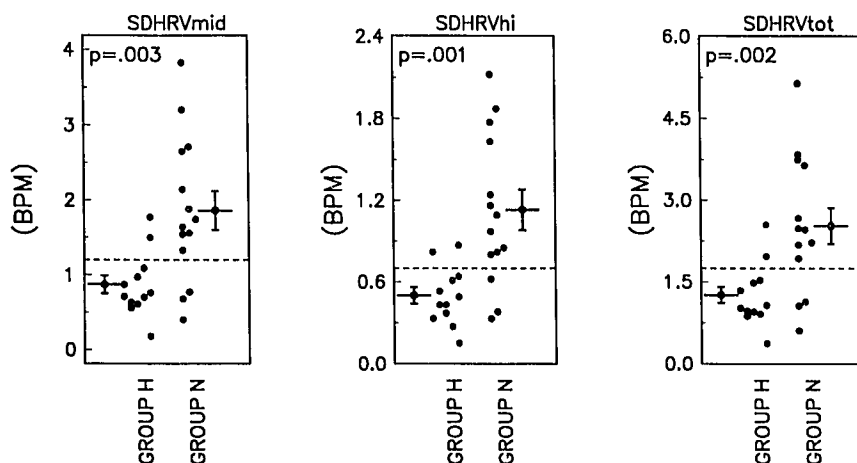


Fig. 8. Autonomic test results for patients in groups H and N. The mean  $\pm$  SEM for each group is depicted by the horizontal line with error bars. The dashed line indicates the critical test value used for each test (table 3).

## REFLEX DYSFUNCTION AND HYPOTENSION

**Table 3. Incidence of Hypotension in Patients with Positive and Negative Autonomic Tests**

Critical Test Value	Positive Test		Negative Test		P*	Sensitivity (%)	Specificity (%)
	n	% Hypotension	n	% Hypotension			
$\Delta$ HR forced breathing $\leq 15$ beats/min	12	83	14	14	0.001	83	83
Valsalva index $\leq 350$ ms	16	69	10	10	0.005	92	69
Modified Valsalva index $\leq 30$ beats/min	14	71	12	17	0.008	83	71
Strain index $\leq 200$ ms	15	67	11	9	0.021	83	67
Modified strain index $\leq 24$ beats/min	16	69	10	10	0.005	92	69
Valsalva ratio $\leq 1.5$	16	69	10	10	0.005	92	69
SDHRV <sub>mid</sub> $\leq 1.2$ beats/min	13	77	13	15	0.005	83	77
SDHRV <sub>hi</sub> $\leq 0.7$ beats/min	13	77	13	15	0.005	83	77
SDHRV <sub>tot</sub> $\leq 1.75$ beats/min	13	77	13	15	0.005	83	77

$\Delta$  HR = change in heart rate; SDHRV = heart rate variability standard deviation (see text).

\* Significance by Fisher's exact test.

with breathing, and high-frequency HRV parameters.<sup>1,25</sup> Both sympathetic and parasympathetic tests were highly significantly different between patient groups (figs. 5–8). This similarity in significance values precludes any conclusions regarding a dominant role of either sympathetic or parasympathetic reflex dysfunction in the development of hypotension after the described induction technique.

Frequency-specific measures of HRV have been shown to provide information on changes in sympathetic-parasympathetic balance during defined experimental and/or clinical interventions (e.g., head-up tilt,<sup>16</sup> mental stress,<sup>38</sup> autonomic blockade,<sup>16,23–25</sup> anesthesia induction,<sup>34</sup> surgical stimulation<sup>39</sup>) and in patients with specific diseases (e.g., myocardial infarction,<sup>12</sup> congestive heart failure,<sup>9</sup> hypertension<sup>6</sup>). Our finding that measures of total HRV (e.g., SDHRV<sub>tot</sub>) were as strongly associated with induction outcome as more frequency-specific measures of HRV (e.g., SDHRV<sub>mid</sub>, SDHRV<sub>hi</sub>) suggests that frequency-specific measures of HRV may offer no advantage in this setting (figs. 7 and 8, table 3). This finding differs from two previous studies in patients having cardiac surgery using preoperative measurements of HRV.<sup>40,41</sup> The study by Estafanous *et al.* documented a significant reduction in high-frequency HRV (but not low-frequency HRV) in patients who developed relative bradycardia after a sufentanil-vecuronium induction.<sup>40</sup> The study by Latson *et al.* suggested that mid-frequency HRV (*vs.* high-frequency HRV and total HRV) was best correlated with hypotension after a sufentanil-midazolam-vecuronium induction.<sup>41</sup> Whether frequency-specific measurements of HRV (*vs.* measurements of total HRV) may provide additional information regarding the influence of ANS

function on the hemodynamic responses to different induction techniques will require additional study.

We found highly significant correlations between HRV parameters and other autonomic tests (figs. 2 and 3, table 1). Correlations were highest when both HRV measurements and other test results were expressed in the common units of beats/minute (*i.e.*, the SDHRV parameters for HRV measurements, and the modified Valsalva parameters for changes in heart rate with the Valsalva maneuver) rather than comparing measurements in other units (e.g., HRV power in (beats/minute)<sup>2</sup>, RR intervals in milliseconds) that are not linearly related. *r* values for the correlations between the modified Valsalva index and the modified strain index with all SDHRV parameters were in the range of 0.77–0.79. The Valsalva ratio was most highly correlated with SDHRV<sub>hi</sub> (*r* = 0.81) compared to both SDHRV<sub>mid</sub> (*r* = 0.68) and SDHRV<sub>tot</sub> (*r* = 0.61). As would be expected, the change in heart rate with forced breathing was most highly correlated with SDHRV<sub>hi</sub> (*r* = 0.76; fig. 3). The correlation between these latter two variables was even higher if the four patients with SDHRV<sub>hi</sub> values above 0.6 beats/min are excluded (*r* = 0.91), suggesting that these two tests are very highly correlated for patients with ANS dysfunction (*i.e.*, patients with decreased high-frequency HRV). Reflecting these significant correlations between autonomic test results, we found similar significance values for group differences in test results for each of these tests of autonomic function (figs. 5–8).

The critical test values for standard Valsalva parameters that were associated with an increased incidence of hypotension in our study were generally less abnormal than those reported in the study by Burgos (e.g.,

a Valsalva ratio of 1.2 in their study *vs.* 1.5 in our study).<sup>1</sup> This difference may reflect the different criteria used for defining hypotension. In the study by Burgos, patients with diabetes were separated into hypotensive and nonhypotensive groups based on whether vasopressors were administered. However, no specific criteria for vasopressor administration were reported. In the present study, we classified patients into hypotensive and nonhypotensive groups based on a decrease in mean blood pressure below a specific value (70 mmHg). We used a specific blood pressure value rather than a percent change from baseline because it is difficult to obtain an accurate baseline in unpremedicated day-surgery patients. Many patients with no history of hypertension had a persistently elevated baseline blood pressure, which was most likely due to patient anxiety. Such patients commonly exhibited a significant decrease in blood pressure relative to this artifactually elevated baseline after induction of anesthesia, but only those patients with ANS reflex dysfunction were likely to have a drop in mean blood pressure to hypotensive levels. Other differences between our study and that of Burgos that may have affected our finding different critical test values include: (1) patients in Burgos's study were premedicated with diazepam and glycopyrrolate, whereas our patients were not premedicated; (2) no patients in Burgos's study were taking  $\beta$  blockers or vasodilators preoperatively; and (3) Burgos's study population was limited to patients with diabetes, whereas our study was performed in unselected day-surgery patients older than 39 yr.

Our results suggest that autonomic test measurements may be a valuable predictor of patients at high risk for development of hypotension. Additional studies with more patients will be needed to determine whether these measurements are a better predictor of hypotension than is patient history of specific medical conditions. It must be noted that the critical test values used in this analysis were determined retrospectively and were determined for a specific induction protocol. It is quite probable that the influence of ANS dysfunction on the occurrence of postinduction hypotension would differ with different induction techniques. If this influence of ANS dysfunction on the occurrence of postinduction hypotension varies with different induction techniques, then simple preoperative screening tests for ANS dysfunction might provide useful information for selection of appropriate induction techniques in high-risk patients. Appropriate techniques in such patients might involve the use of different primary in-

duction agents or simply might involve reduced dosages or slower titration of the same induction agents.

Although most commercial monitors do not provide beat-to-beat measurements of heart rate in graphical format, it would not be difficult to add this capability. Such beat-to-beat graphs could be used to perform any of several preoperative screening tests for ANS dysfunction with minimal additional effort by the clinician (*e.g.*, modified Valsalva index, modified strain index, Valsalva ratio, change in heart rate with forced breathing, visual estimation of HRV). The capability for analytical measurements of HRV would require more extensive changes, but several monitoring companies are considering this option for use in intensive care unit settings. The potential advantage of HRV measurements is that they do not require patient effort.

In summary, our results suggest that: (1) some degree of ANS reflex dysfunction is not uncommon in patients older than 39 yr presenting to our day-surgery unit, and (2) this ANS reflex dysfunction is associated with an increased incidence of hypotension when using the described induction technique. Patients with ANS dysfunction could be identified by a variety of simple, noninvasive tests. Whether preoperative use of such tests might provide useful clinical information for the selection of specific induction techniques in high-risk patients will require additional study.

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## REFLEX DYSFUNCTION AND HYPOTENSION

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