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Increased Intraoperative Cardiovascular Morbidity in Diabetics with Autonomic Neuropathy

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Thirty-eight consenting subjects scheduled for elective ophthalmologic surgery were classified as nondiabetics (n = 21) or diabetics (n = 17) and were tested preoperatively for autonomic dysfunction. The autonomic tests consisted of respiratory sinus arrhythmia and heart rate responses to the Valsalva maneuver to test cardiac vagal function and diastolic blood pressure responses to head-up tilt and cold pressor test to assess sympathetic efferent integrity. At a separate time, anesthesia was established with fentanyl (2 μg/kg), sodium thiopental (3–5 mg/kg), and vecuronium (0.1 mg/kg), and maintained with isoflurane, oxygen, and nitrous oxide. An anesthesiologist, blinded to the autonomic test results, recorded perioperative blood pressure and heart rate. The autonomic test results revealed significant autonomic dysfunction among the diabetics. Heart rate and blood pressure declined to a greater degree ($P < 0.05$) during induction of anesthesia in diabetics compared with controls and there was less of an increase in these same parameters following tracheal intubation in diabetic patients. Thirty-five percent of diabetics required intraoperative vasopressors compared with only 5% of control patients ($P < 0.05$). A major finding was that the diabetics who required intraoperative blood pressure support had significantly greater impairment of autonomic test results compared with those diabetics who did not need vasopressors. Diabetics are at increased risk for cardiovascular lability during anesthesia and preoperative screening of diabetics with simple noninvasive autonomic tests may be useful in identifying those at high risk for perioperative cardiovascular instability. (Key words: Anesthesia: general. Complications, diabetes: autonomic dysfunction.)

DIABETES MELLITUS is often associated with cardiovascular abnormalities, many of which are due to atherosclerotic changes in the coronary and peripheral arteries. Coronary heart disease is considered the principal cause of death among diabetics.[1,2] Other cardiovascular abnormalities have often been attributed to diabetic autonomic neuropathy. There is an increased mortality rate among diabetics with autonomic neuropathy, and there have been several reports of sudden death, which have not been associated with myocardial infarction based upon postmortem examinations.[3,4]

Several case reports have suggested that the diabetic patient undergoing surgery may have a higher incidence of undesirable cardiovascular events than the general population. These events include bradycardia and hypotension unrelated to blood loss as well as unexplained cardiorespiratory arrest during the perioperative period. Some of these diabetic patients were noted retrospectively to have severe autonomic neuropathy.[5–7]

In the present prospective study, we examined diabetic patients: 1) to determine whether there is an association between autonomic neuropathy and perioperative cardiovascular instability; 2) to identify which periods of time during the perioperative period are associated with the greatest hemodynamic lability; and 3) to determine if preoperative autonomic tests might be used to predict diabetic patients at greatest risk of cardiovascular events during anesthesia and surgery.

Materials and Methods

This study was approved by the Institution's Human Research Review Committee. Consecutive patients providing informed consent were evaluated. Seventeen diabetic and 21 nondiabetic control patients scheduled for elective ophthalmologic surgery participated in this study. Each patient underwent preoperative evaluation, which included a history, physical examination, 12 lead ECG, chest x-ray, and blood chemistry screening. Patients with history of previous myocardial infarction of less than 6 mo duration, myocardial revascularization, carotid endarterectomy, TIA or stroke, or significant renal disease (serum creatinine greater than 1.5 mg/dl) were excluded from this study.

The range of ages were considerable; however, the average ages of the control and diabetic groups were comparable (table 1). There were six female and 11 male diabetics and seven female and 14 male control patients. Fifteen diabetic patients were receiving insulin therapy; 13 for more than 10 yr. Seven diabetics and seven control patients were treated with antihypertensives. None of the study patients were taking beta adrenergic antagonists, peripheral vasodilators, or central sympatholytic agents. Four diabetics and one control patient had prior myocardial infarction based on history and ECG. None had signs or symptoms of heart failure or unstable cardiac symptoms. Fourteen diabetics and 17 controls had retinopathy. Among the diabetics, eight had clinical evidence of peripheral neuropathy, eight complained of gastrointestinal symptoms such as esophageal reflux (n = 4),

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TABLE 1. Resting Cardiovascular Parameters

Group	Sample Size	Age	Heart Rate (beats/min)		Mean Arterial Pressure (mmHg)	
			Baseline	Pre-induction	Baseline	Pre-induction
Young controls	9	29.7 ± 2.9	57.8 ± 2.9*†	64.2 ± 6.2*	80.6 ± 1.6†¶	93.3 ± 3.2†§¶
Older controls	12	67.4 ± 2.3	68.8 ± 3.8	83.5 ± 3.9§	91.9 ± 2.5	109.7 ± 3.6§
All controls	21	51.2 ± 4.5	64.1 ± 2.7‡	75.8 ± 3.9§	87.1 ± 2.0**	103.1 ± 3.1§
All diabetics	17	51.0 ± 4.6	73.2 ± 2.6	77.6 ± 2.9	97.3 ± 3.1	112.9 ± 5.8§

Data are mean ± SEM. Significant differences between groups are as follows:
* $P < 0.05$, young *versus* older controls.
† $P < 0.01$, young controls *versus* diabetics.
‡ $P < 0.05$, all controls *versus* diabetics.
§ $P < 0.01$, baseline *versus* pre-induction.
¶ $P < 0.01$, young *versus* older controls.
** $P < 0.01$, all controls *versus* diabetics.

heartburn (n = 2), nausea and vomiting (n = 2), and two complained of dizzy spells. There were eight type I and nine type II diabetic patients. The duration of time from diagnosis of diabetes to study averaged 19.3 yr (range, 5 mo to 31 yr). Fifteen of 17 patients were receiving insulin therapy; one was diet-controlled and one was taking an oral hypoglycemic agent. The duration of insulin therapy ranged from 1 mo to 31 yr.

AUTONOMIC TESTING

Standard noninvasive autonomic tests (respiratory sinus arrhythmia,[8-10] Valsalva's maneuver,[11,12] head-up tilt,[11-13] and cold pressor test[11,14] were carried out at least 1 day prior to scheduled surgery on each patient. Following familiarization with the tests, subjects lay supine for 20 min. Blood pressure was determined with a standard arm cuff and single observer auscultation of Korotkoff sounds. Heart rate (HR) was detected from lead II of the ECG. A 2-min period of quiet breathing was observed with ECG displayed on an oscilloscope and simultaneously recorded on FM magnetic tape for later analysis of respiratory sinus arrhythmia (RSA). This was followed by a period of forceful breathing, which consisted of 1 min maximum inspiratory and expiratory efforts (each 5 s in duration) at a breathing frequency of 6/min.

A 10-min supine recovery period was then observed followed by two consecutive Valsalva maneuvers. These consisted of blowing into a mouthpiece connected to a sphygmomanometer. The interposing tubing had a 22-g needle inserted so that an open glottis was required to maintain the blowing pressure. Subjects began blowing at normal end-inspiration, maintained 40 mmHg of positive pressure for 15 s, released the pressure rapidly, and then breathed quietly for 1 min. The control R–R interval was taken as the average of ten intervals immediately prior to blowing. Phase III of the Valsalva maneuver was the shortest interval occurring immediately after release of Valsalva strain, whereas Phase IV was the longest interval occurring within 30 s of release of blowing. These intervals were used to calculate the strain response (change from control to Phase III), Valsalva ratio (Phase IV/III), and Valsalva index (Phase IV–III).

The tilt response was studied after a 5-min recovery period. Blood pressure and HR were determined every 2 min during a 6-min control period and a 6-min 65° head-up tilt. Blood pressures and cardiac intervals were averaged during control and tilt periods.

A 5-min recovery period was observed, followed by a 6-min precold control period. Blood pressures and R–R intervals were recorded every 2 min during this control period and averaged. The nondominant hand was placed (up to the wrist) in a bucket of ice water (3–4° C) for 1 min. Blood pressures and cardiac intervals were determined during the last 20 s of cold exposure.

The taped ECG data were analyzed by a blinded investigator during a later session. The standard deviation of 100 consecutive R–R intervals determined by computer was taken as an index of RSA during both quiet and forceful breathing periods. Cardiac intervals were determined for control and stress periods of the tilt, Valsalva, and cold pressor tests.

The autonomic tests, which are highly specific for assessing cardiac vagal integrity, consisted of quiet and forceful breathing RSA, the Valsalva ratio, and the Valsalva index. The test results that are influenced primarily (but not solely) by the sympathetic nervous system consisted of HR increases during the Valsalva strain and head-up tilt and the diastolic blood pressure increases provoked by tilt and cold pressor tests.

ANESTHETIC TECHNIQUE

The results of the autonomic tests were not known to the anesthesiologist at the time the patients were anesthetized for their eye surgery. Anesthetic technique was standardized for each patient. Premedication consisted of oral diazepam (5–10 mg approximately 1 h prior to induction) and glycopyrrolate (0.2 mg) administered iv upon arrival in the holding area of the operating room. Fentanyl (2 μg/kg) and sodium thiopental (3–5 mg/kg) were utilized for induction of anesthesia. Vecuronium (0.1 mg/kg) was used to facilitate endotracheal intubation. A nerve stimulator (Puritan-Bennett NMT Monitor 221®) was utilized to monitor neuromuscular blockade. Endotracheal intubation was performed when the twitch height

TABLE 2. Autonomic Test Results: Vagal Function

Group	Respiratory Sinus Arrhythmia (ms)		Valsalva R–R Intervals (ms)	
	Quiet Breathing	Forceful Breathing	Phase IV–III	Phase IV/III
Young controls	51.5 ± 4.4*†	117.4 ± 21.3*†	457.4 ± 45.5*¶	1.68 ± 0.09*
Older controls	28.0 ± 5.8	49.6 ± 9.8	295.1 ± 62.2**	1.49 ± 0.12**
All controls	38.1 ± 4.6‡	78.7 ± 12.8§	364.7 ± 43.5§	1.57 ± 0.08§
All diabetics	21.7 ± 4.8	35.2 ± 7.9	133.1 ± 18.0	1.21 ± 0.03

Data are mean ± SEM. Significant differences between groups are as follows:
* $P < 0.01$, young controls *versus* diabetics.
† $P < 0.01$, young *versus* older controls.
‡ $P < 0.05$, all controls *versus* diabetics.
§ $P < 0.01$, all controls *versus* diabetics.
¶ $P < 0.05$, young *versus* older controls.
** $P < 0.05$, old controls *versus* diabetics.

was reduced by 90–100%. The average time for intubation was less than 30 s. Anesthesia was maintained with isoflurane (0.75–1.25%), nitrous oxide (50%), oxygen, and vecuronium. Reversal of residual muscle paralysis was achieved with neostigmine (3–5 mg) and glycopyrrolate (0.6–1.0 mg). Intraoperative blood glucose ranged from 142 to 350 ng/dl. Those with values above 300 mg/dl were treated with sliding scale iv insulin.

An automated noninvasive oscillometric blood pressure recording device (with printout) was used to determine blood pressure and HR every minute during the pre-intubation period until 10 min after intubation and every 5 min for the remainder of surgery. Mean arterial blood pressure (MABP) and HR were averaged during the pre-induction period. The peak changes in these parameters during induction and intubation were determined. The MABP and HR during each hour of surgery (beginning from 10 min after intubation) were averaged. For each subject, the coefficient of variability of these parameters were determined hourly and used as intraoperative cardiovascular variability indices. Individual standard deviations of consecutive 5-min HR and blood pressure readings were divided by mean hourly values and multiplied by 100 to obtain the coefficient of variation for each hour of surgery. The use of vasopressors (for systolic blood pressure < 90 mmHg) and other pharmacologic agents were noted.

STATISTICAL METHODS

Comparisons between groups were performed with Student's unpaired *t* test, chi-square, and analysis of variance. The diabetic and control groups were also divided into young (<45 yr) and older age (≥45 yr) groups and compared. *P* values less than 0.05 were considered significant.

To seek a relationship between autonomic function and intraoperative hemodynamics, linear regression and correlations were sought between autonomic test results and blood pressure and HR responses to induction, intubation, and the variability indices during each hour of surgery. In addition, the diabetics were divided into two groups: those who required intraoperative vasopressors and those who did not. The autonomic test results were averaged for each of these groups and compared with unpaired *t* tests. Critical values for each test were chosen that resulted in the highest sensitivity and specificity when employed for retrospective identification of diabetics who developed intraoperative hypotension.

Results

The average age of the control (51.2 ± 4.5 yr) and diabetic (51.0 ± 4.6 yr) groups (mean ± SEM) were similar (table 1). Each study group was subdivided into young and older age groups and statistical analyses were performed. We were unable to discern a significant age effect among the diabetics in the autonomic test results or in the intraoperative responses; therefore, further analyses were performed using the diabetic group as a whole and comparing this group to both the subdivided (younger and older) control group and the combined control group.

Table 1 shows baseline HR and MABP obtained during a quiet supine rest period during the autonomic testing session and pre-induction values obtained in the operating room. Baseline HR and MABP and preinduction MABP were observed to be significantly higher among the diabetics compared with all controls. Heart rate and MABP increased significantly from baseline during the pre-induction period in all the control patients. Among the diabetics, the pre-induction MABP was significantly higher compared with baseline values, but the HR was not significantly changed. Among the control patients, age-related differences in both baseline HR and MABP were noted (table 1).

The response to the autonomic tests were divided into those dependent primarily on cardiac vagal efferent function (table 2) and those associated with sympathetic efferent function (table 3). Within the control group, a significant age-related effect was seen in the HR response to quiet and deep breathing and Valsalva strain but not in the Valsalva ratio (table 2). The RSA was significantly less among the diabetics compared with that in controls. The Valsalva ratio and the Valsalva index were significantly less in the diabetics than either the younger or older control groups. The results also demonstrate that the

TABLE 3. Autonomic Test Results: Sympathetic Function

	Δ RR Interval (ms)		Δ Diastolic Pressure (mmHg)	
	Valsalva	Tilt		
Group	Control to Phase III	Control to Stress	Tilt	Cold
Young controls	−166.4 ± 25.1	−221.4 ± 32.0‡§	3.7 ± 1.3**	19.6 ± 4.2
Older controls	−200.0 ± 23.7*	−111.1 ± 19.0	1.6 ± 1.5	12.9 ± 1.5
All controls	−185.6 ± 21.4†	−158.4 ± 20.9¶	2.5 ± 1.0†	15.6 ± 2.0
All diabetics	−114.1 ± 17.4	−87.4 ± 13.5	−1.5 ± 1.7	11.4 ± 2.0

Data are mean ± SEM. Significant differences between groups are as follows:
* $P < 0.05$, old controls *versus* diabetics.
† $P < 0.05$, all controls *versus* diabetics.
‡ $P < 0.01$, young controls *versus* diabetics.
§ $P < 0.01$, young *versus* older controls.
¶ $P < 0.01$, all controls *versus* diabetics.
** $P < 0.05$, young controls *versus* diabetics.

older controls were less well differentiated from the diabetics than were the younger controls.

The tests of sympathetic integrity revealed that the diabetics had less tachycardia (compared with controls) in response to the Valsalva strain and head-up tilt (table 3). The diastolic blood pressure of the diabetics decreased during head-up tilt, whereas the controls had increases in diastolic pressure. These responses were significantly different.

Within the control group, an age-related diminution of the HR response to head-up tilt was noted. The diastolic blood pressure responses to head-up tilt and cold were less in the older compared with those in the younger controls. Statistical examination of the data based upon preoperative blood pressure failed to reveal a greater blood pressure lability in the hypertensive subjects compared with normotensive controls and diabetics.

We were unable to demonstrate significant differences in the coefficient of variation of HR and MABP during consecutive hours of surgery among the controls and diabetics (data not shown). However, MABP responses to induction of anesthesia and tracheal intubation differed between groups (fig. 1). MABP decreased an average of 30 mmHg during induction and increased only 7 mmHg (above baseline) with tracheal intubation in the diabetic group. The decrease in MABP was greater and the subsequent increase was less than in the control group. A similar but nonsignificant trend was noted in the HR responses (fig. 1). There were no differences in HR and MABP responses to reversal of neuromuscular blockade, emergence from anesthesia, tracheal extubation, and recovery room stay among groups. Furthermore, there were no significant cardiovascular events noted postoperatively in either group.

After the initial responses to tracheal intubation, there were no further significant episodes of intraoperative hypertension (SBP > 160) noted. However, intraoperative vasopressors (neosynephrine or ephedrine) were required to treat intraoperative hypotension (systolic blood pressure of less than 90 mmHg). Six diabetic patients (six of 17, or 35%) and one control patient (one of 21, or 5%) required intraoperative vasopressors (significantly different by chi-square analysis, $P < 0.05$). In most instances (five of six) the decrease in blood pressure occurred after tracheal intubation and before surgical stimulation. The autonomic test results of the six diabetic patients who required intraoperative vasopressors were compared with those of 11 diabetics who did not require blood pressure

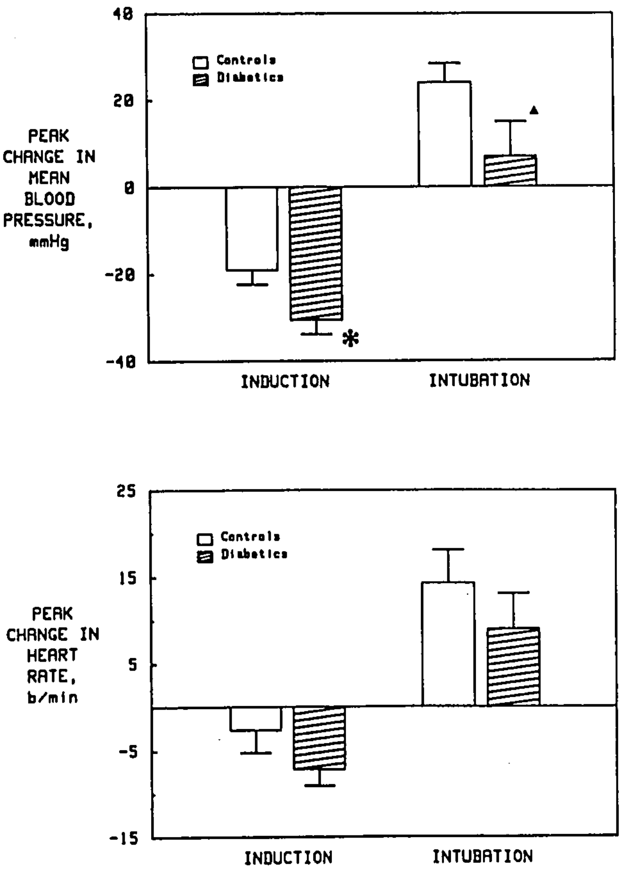

FIG. 1. MAP declined significantly from awake baseline in controls and diabetics after anesthetic induction. This decline was larger among the diabetics (*$P < 0.05$). Increases in pressure following intubation were less in the diabetics (▲, $P < 0.06$). Similar trends were noted in the HR responses of these two groups.

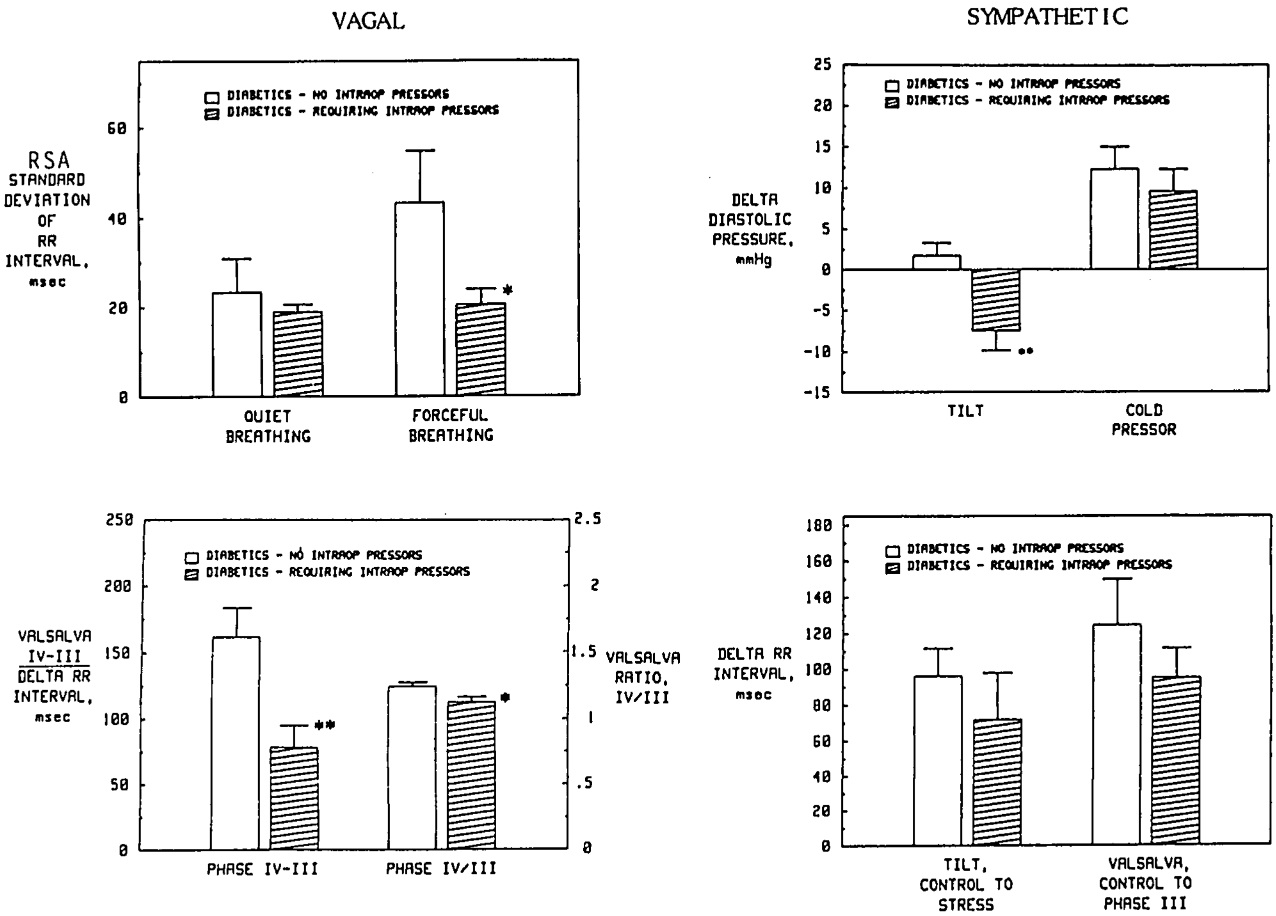

FIG. 2. Comparison of autonomic test results of the diabetic patients who required vasoactive drugs for intraoperative blood pressure support with those of diabetics who did not require such support. Results of test of vagal function are shown in the two left graphs, whereas sympathetic test results are shown on the right. Significantly different test results between groups: *$P < 0.05$ and **$P < 0.01$.

support (fig. 2). There were significantly different responses noted in three of the autonomic tests. These were the HR response to the Valsalva maneuver (Valsalva ratio and index), the forceful RSA, and the diastolic blood pressure increase in response to the tilt. The remaining autonomic tests showed similar but nonsignificant trends for diminished responses in diabetics who required intraoperative vasopressors.

The autonomic tests that best differentiated the diabetics at risk were examined, and critical cutoff values for each test result were derived. These were chosen to provide the highest sensitivity and specificity for future screening of diabetics (table 4). If diabetics in our study had two of four deficient responses (below the cutoff value), no false-negatives (100% sensitivity) would have occurred, but there would have been a 46% false-positive rate (54% specificity) in applying these screening tests to predict those who had intraoperative hypotension. If the criteria were changed so that three of four test results below their cutoff values were required to classify individuals at risk, there would have been a 17% false-negative rate (83% sensitivity) and an 18% false-positive rate (82% specificity).

Discussion

Diabetes is a disease that affects multiple organ systems including cardiovascular, renal, and neurologic systems. These sequelae increase the likelihood that diabetics will require surgery. It is estimated that 50% of diabetics will

TABLE 4. Critical Values for Screening Diabetics

Test	Cutoff*	Sensitivity (%)	Specificity (%)
Forceful breathing RSA	<30 ms	100	54
Valsalva ratio	≤1.2	83	54
Valsalva index	<123 ms	83	72
Tilt, change in diastolic pressure	< −5 mmHg	66	81

* Measured variable chosen to best divide diabetics who required intraoperative vasopressors from those who did not.

require some type of surgical procedure in their lifetime.[15] In addition to the multiorgan involvement, autonomic neuropathy is reported to be present in 20–40% of all diabetics,[16–18] and this has several implications important to the anesthesiologist. Esophageal dysfunction and gastric hypotonia may be present,[19–21] which may increase the risk of regurgitation and aspiration in the perioperative period.[22] In addition, severe impairment of baroreflex function leading to orthostatic intolerance and significant blood pressure lability can occur.[8,9] Bradycardia, hypotension, and cardiopulmonary arrest have been reported among diabetics with autonomic neuropathy during the perioperative period.[5–7] Hemodynamic instability is not well tolerated in this population because many have underlying heart disease secondary to diffuse small-vessel coronary disease and painless myocardial infarction.[23]

We applied routine autonomic stress tests to a group of diabetics without renal disease and with minimal cardiac disease. Almost all diabetics had retinopathy and several were being treated for mild hypertension. We also examined a group of controls, similar in many respects except for the absence of diabetes. Only patients scheduled for ophthalmologic surgery were included in this study. This type of surgery is not associated with significant changes in intravascular volume. Therefore, perioperative events could be more specifically attributed to either the patient's underlying disease processes, the anesthetic agents used for induction and maintenance, or the response to nonsurgical stimuli, such as laryngoscopy and tracheal intubation.

The autonomic tests employed in this study (especially respiratory sinus arrhythmia tests) are known to be more specific for assessing parasympathetic function than sympathetic function.[8,9] Tachycardia during Phase III of the Valsalva and during head-up tilt is not solely due to efferent cardiac sympathetic excitation; cardiac vagal withdrawal is undoubtedly involved, while diastolic pressure increases during head-up tilt[11–13] and the hypertension in response to the cold pressor test are reported to be mediated primarily by peripheral sympathetic responses.[14]

The diabetic patients in this study had significantly impaired responses to the autonomic tests compared with the responses of the control population. However, no age effect was noted within the diabetic group. Aging is known to be associated with diminished autonomic reflex function,[12,13] and it was not surprising to find diminished autonomic responsiveness among the older controls. The failure to discern an age effect among the diabetics is probably related to the tremendous variation and age-independent effect of onset and progression of autonomic neuropathy in this group.

We sought to determine if perioperative blood pressure lability was related to autonomic dysfunction among diabetic patients. We conjectured that the presence of autonomic dysfunction in combination with anesthetic-induced attenuation of autonomic reflexes could predispose diabetic patients to perioperative hypotension and inappropriate bradycardia. These events have been associated with ischemic damage to the heart, kidney, and brain. Our data indicate that 35% of diabetic patients required intraoperative blood pressure support, and these diabetics had the most deficient responses to autonomic stress tests. Only one of these episodes was due to bradycardia that responded to atropine, and this was unrelated to manipulation of the eye. None of these hypotensive episodes resulted in clinically evident intraoperative or postoperative ischemic insults to any organ system, presumably because episodes were recognized and treated promptly.

During preoperative autonomic testing, supine baseline HR and blood pressure were increased among the diabetics compared with those in both young and old control patients. Resting tachycardia is not uncommon in diabetics.[10,24] This has been attributed to vagal or combined vagal and sympathetic neuropathy. There are other possible causes of an increased resting HR in diabetics, such as effects related to insulin therapy.[25] The incidence of hypertension among diabetics has been reported to be between 29% and 54%, which is consistent with our data.[26,27] This hypertension may be related to autonomic imbalances affecting cardiac output, atherosclerotic changes in the peripheral vasculature, or abnormal sodium retention among the diabetics.[27]

The perioperative data indicate that the period of highest risk for hypotension and bradycardia in diabetics is the first several minutes after tracheal intubation. Cardiovascular changes associated with induction of anesthesia are primarily due to sodium thiopental, which is known to decrease central vagal outflow, dilate vascular smooth muscle, depress the myocardium, and diminish baroreflex function.[28–30] The data shown in figure 1 indicate that following induction the blood pressure and HR of diabetics decreased more than in the nondiabetic controls. Furthermore, laryngoscopy and intubation stimulate laryngeal and upper airway reflexes and increase sympathetic efferent activity,[31] resulting in less tachycardia and hypertension in the diabetics. These altered responses may be related primarily to underlying autonomic neuropathy in the diabetics because fluid status and other disease processes were similar in the diabetic and control groups. Autonomic reflexes, *i.e.*, vasoconstriction and tachycardia, fail to completely compensate for the direct vasodilating effects of sodium thiopental in diabetics. Diabetics also had attenuated reflex responses to laryngoscopy. These factors promote postintubation hypotension and relative bradycardia (especially in diabetics with advanced autonomic neuropathy).

The standard autonomic tests employed in the present study were reasonably sensitive. However, a high specificity (few false-positives) was obtained only when criteria from three autonomic tests were combined to define diabetics at risk. Unfortunately, the requirement of several preoperative screening tests may make the routine use of autonomic tests less practical. However, it is probable that some simple form of autonomic screening combined with clinical history might prove useful. This will require prospective validation.

It is important to note that the incidence of perioperative hypotension in diabetic patients may be greater than the rate of 35% noted in the present study. We studied relatively healthy diabetics who were receiving a minimum of vasoactive medications. None had advanced renal or cardiac disease. It is likely that the incidence of cardiovascular instability during anesthesia and surgery is higher among the general population of diabetic patients. Furthermore, hypotensive episodes may lead to more catastrophic events in the less healthy diabetic population.

In summary, the current study indicates that the presence of diabetic autonomic neuropathy is associated with an increased risk of perioperative cardiovascular instability. Our data suggest that preoperative autonomic screening tests can identify a subset of diabetics who are at risk. The period of highest risk appears to be after induction and before surgical incision. Although the routine use of autonomic screening of diabetics may be impractical, the information obtained from such testing could prove useful to the anesthesiologist when planning the anesthetic management of these patients.

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