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PATTERN AND PREVALENCE OF CARDIOVASCULAR AUTONOMIC NEUROPATHY IN DIABETICS VISITING A TERTIARY CARE REFERRAL CENTER IN INDIA

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Abstract : The cardiovascular autonomic neuropathy (CAN) is a known complication of long standing diabetes. In the present study, the prevalence of sympathetic and parasympathetic abnormalities in diabetic patients was evaluated on retrospective analysis of standard tests done for the assessment of CAN. Three different scoring systems were utilized for assessment of CAN namely, Ewing's crtieria, Bellavere's criteria and the criteria followed at the Autonomic Function Test laboratory. All the three criteria use different set of tests for classification. A total of 124 patients' laboratory data was analysed. The abnormality of single test ranged from 6.49% in Valsalva Maneuver to 47.41% in cold pressor test. When Bellavere's criteria was used only 53 patients had evidence of CAN while Ewing's criteria revealed that 100 patients had CAN however 69 of these patients could not be categorized. The criteria used by AFT laboratory revealed that isolated sympathetic (49 patients) and paraysmpathetic (10 patients) abnormality can be seen in CAN along with those with combined deficits (42 patients). If the Bellavere's criteria is used then patients with dominant sympathetic neuropathy are likely to be missed during testing. High prevalence of CAN in tertiary care referral centre suggests that the testing of autonomic functions in diabetics should be done routinely. It is recommended that full battery of test to evaluate both the arms of autonomic drive namely sympathetic and parasympathetic should be done and reported as such.

Key words : diabetic neuropathy autonomic function

INTRODUCTION

Long standing diabetes mellitus is associated with micro and macro level dysfunction in multiple organ systems. Diabetic autonomic neuropathy may manifest as disturbances in cardiovascular, gastrointestinal or genitourinary system (1). Diabetic autonomic neuropathy is often an ignored complication of diabetes as the

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symptoms associated with it are generally mild and are not life threatening.

Cardiac autonomic neuropathy (CAN) is one of the major complications of diabetes mellitus. It is also the most under diagnosed and least understood diabetic complications (2). It generally manifests as exercise intolerance, resting tachycardia and orthostatic hypotension. Though these manifestations themselves are not life threatening, studies have revealed an increase in all cause mortality in the diabetic patients with CAN (1). Meta-analysis of 15 studies has demonstrated the direct association between the presence of CAN and mortality (3). The pooled estimate based on 2,900 subjects was 2.14 with 95% CI of 1.83–2.51 (3). The authors reported a relative risk of mortality of 3.4 if two or more abnormalities were found in the tests for CAN as compared to 1.2 if only one test was abnormal. The reason for high mortality is not clear though it has been suggested that neuropathy, accelerated nephropathy, association with microangiopathy and disturbed cardiovascular risk profile are important contributors.

The presence of CAN is diagnosed on the basis of tests of autonomic reactivity. The criteria for the diagnosis were laid by Ewing (4) and Bellavere (5). Ewing's criteria was based on tests for parasympathetic as well as sympathetic components (5 tests) while Bellavere's criteria was based only on the tests of parasympathetic components (3 tests). The American Diabetes Association and American Academy of Neurology utilizes the Bellavere's criteria for diagnosis of CAN (6).

The reported prevalence of diabetic CAN is varied. This is generally due to the differences in the criteria used for the diagnosis of CAN and differences in patient cohort i.e. community based study or referral centre study (1). The reported prevalence ranges from 7.7% in newly diagnosed diabetes to a high of 90% in potential recipients of a pancreas transplant (1).

According to WHO the burden of diabetes mellitus in India is 31.7 million (approximately 3% population) and projected figure for 2030 is 79.44 million (7). Our laboratory has earlier published the prevalence of CAN in recently diagnosed diabetics (8). In the present analysis the prevalence of CAN in the patients of diabetes mellitus was evaluated in a tertiary referral centre using commonly used criteria namely Ewing and Bellavere. Additionally, CAN was also classified on the basis of parasympathetic and sympathetic involvement as suggested by San Antonio Consensus Panel (1988) and practiced in the Autonomic Function Laboratory, Department of Physiology, AIIMS.

Patients and Methods

The study was carried out at the Autonomic Function Test (AFT) laboratory of the Department of Physiology, All India Institute of Medical Sciences, New Delhi. Consecutive patients of diabetes mellitus who were referred to the AFT laboratory from January 2008 to June 2009 were included in the study. For each patient, the results of the standardized test were taken from the laboratory records. On the basis of the test results, each patient was scored for CAN.

The criteria for considering test as normal, borderline or abnormal is shown in Table 1. All the five tests as described by Ewing were done. For many tests, age specific cutoffs have been published but in the present analysis age specific cutoff were not used as the primary purpose was to compare the three routinely used scoring systems for detection of CAN. The hospital records and OPD records were searched for the HbA1c and duration of diabetes.

Test for assessment of cardiovascular autonomic status

The test for the assessment of CAN was done as per standard protocols published in literature (10, 11, 12, 13) and practiced in the AFT laboratory, AIIMS.

Deep breathing test (respiratory sinus arrhythmia)

The heart rate and respiration monitoring was done from the ECG recordings and sthethographic respiratory tracings recorded on the polygraph (POLYRITE-4, Recorders and Medicare System, India). A baseline recording of ECG and respiration was taken for 30 seconds. The subject was asked to take slow and deep inspiration followed by slow and deep expiration such that each breathing cycle lasted for 10 seconds. Calculation was done from the tracing of respiration and ECG. The changes in the heart rate between inspiration and expiration were averaged over 6 cycles.

Valsalva Maneuver

It was done in sitting position. The patient was instructed to blow into a mouth piece attached to sphygmomanometer. The expiratory pressure was kept at 40 mmHg for 15 seconds. At the end of 15 seconds the subject was asked to release the pressure. Valsalva Ratio was calculated from the longest RR interval during phase IV and shortest RR interval during phase II.

Handgrip test

The baseline blood pressure was recorded. The subject was asked to press a handgrip dynamometer at 30% of maximum voluntary contraction for 4 minutes. The blood pressure was recorded at 1st, 2nd and 4th minute of contraction. The rise in the diastolic pressure above the baseline was noted.

Cold pressor test

The baseline blood pressure was recorded. The subject was instructed to immerse the right hand in the cold water (10 degree Celsius) for 1 minute upto the wrist. The blood pressure was measured at the end of one minute. The rise in the diastolic pressure over baseline was noted.

Lying to standing test

The blood pressure and the ECG was recorded in supine position. The subject was instructed to attain standing posture in 3 seconds. The ECG was continuously recorded during the procedure. The blood pressure was measured at 0.5th, 1st, 2nd, 2.5th and 5th min. 30:15 ratio was calculated from ECG. It is the ratio of RR interval at 15th beat and RR interval at 30th beat. The fall in systolic blood pressure was calculated.

Head up tilt test (HUT)

Subject was asked to lie down on a head up tilt table for 5 minutes and supine blood pressure was measured. The table was tilted in 15 seconds for 70° (4.8 deg/sec) and kept in that position for 5 minutes. The subject was asked to stand on the foot rest (passive standing). The maximum fall within 5 minutes of orthostasis was noted.

Patients were scored and categorized as follows :

1. Categorization as per Bellavere criteria (4)

Tests used for scoring (Table I)

1. Deep breathing test (delta heart rate)
2. Valsalva maneuver (Valsalva Ratio)
3. Lying to standing (30:15 ratio)

The scores were added and CAN was classified as follows

0 – 1 = no CAN

2 – 3 = early CAN

4 – 6 = definite CAN

2. Categorization as per Ewing's method (5)

Tests used for scoring: All the tests except cold pressor test.

The scores were added and CAN was classified as follows :

Normal = all tests normal or 1 test borderline.

Early = one of the three heart rate tests abnormal or two borderline.

Definite = two heart tests abnormal.

Severe = two heart tests abnormal + one or both BP tests abnormal.

TABLE I : Test for assessment of autonomic function with cut-off limits (4, 5).

Test	*Parameter*	*Criteria*	*category*	*Score*
Deep breathing test (DBT)	Delta heart rate (bpm)	> 15	Normal	0
		11–14	Borderline	1
		< 10	Abnormal	2
Valsalva Maneuvre (VM)	VR	> 1.21	Normal	0
		1.11–1.20	Borderline	1
		< 1.10	Abnormal	2
Handgrip test (HGT)	Change in diastolic blood pressure (mmHg)	> 16	Normal	0
		11–15	Borderline	1
		< 10	Abnormal	2
Cold pressor test (CPT)	Change in diastolic blood pressure (mmHg)	> 16	Normal	0
		11–15	Borderline	1
		< 10	Abnormal	2
Lying to standing test (LST) /Head-up tilt (HUT)	Fall in systolic pressure* (mmHg)	< 10	Normal	0
		11–20	Borderline	1
		> 20	Abnormal	2
	30 : 15 ratio	> 1.04	Normal	0
		1.01–1.03	borderline	1
		< 1.01	Abnormal	2

*Ewing's original criteria for abnormal was fall more than 30 mmHg. The criteria were modified in line with current definition of orthostatic hypotension (9).

†CPT is not included in other mentioned criteria: it is done as an additional test in AFT laboratory, AIIMS with the criteria mentioned.

3. Categorization as per Autonomic Function Laboratory, AIIMS (8)

Tests for parasympathetic component

1. Deep breathing test (delta heart rate)
2. Valsalva maneuver (Valsalva Ratio)
3. Lying to standing (30:15 ratio)

Tests for sympathetic component

1. Lying to standing (change in systolic blood pressure)
2. Handgrip test (change in diastolic blood pressure)
3. Cold pressor test (change in diastolic blood pressure)

Scoring for parasympathetic and sympathetic component

Normal = all test normal or one test borderline.

Early = one test abnormal or two test borderline.

Definite = two tests abnormal.

RESULTS

One hundred and twenty four patients of diabetes mellitus were referred to Autonomic Function Laboratory, AIIMS from different clinical departments for autonomic function testing between January 2008 to July 2009. The demographic profile of the patients is shown in Table II.

Autonomic function tests

Out of 124 patients, all the tests could be performed only in 76 patients. Some patients could not perform the test requiring physical effort namely, Valsalva maneuver, hand grip test and deep breathing test. Valsalva maneuver was not done in patients with diabetic retinopathy. Cold pressor test was not done in patients with associated coronary artery disease. Table III shows the results for each test in the patients on the basis of criteria mentioned in the Table I.

The Tables IV, V and VI shows the scoring based on Bellavere, Ewing and AFT lab

TABLE II: Demographic profile of the patients.

Parameters	*Patients (n=124)*
Age (years)*	45.36±13.35
Male : Female (n)	79:46
Systolic BP (mmHg)*	123.08±19.41
HbA1c (n=39)*	7.62±1.95
Duration of DM (months) (n=39)†	3(1–12)

*Values are expressed in Mean±SD.
†Values are expressed in median (1st–3rd quartile)

TABLE III: Results for each test done in the patients.

Test	*Parameter*	*Total*	*B*	*Ab*	*% Ab*
Deep breathing test	Delta heart rate	124	26	43	34.67
Valsalva Maneuver	Valsalva ratio	077	04	05	06.49
Handgrip test	Rise in diastolic pressure	122	26	56	45.90
Cold pressor test	Rise in diastolic pressure	116	26	55	47.41
Head up tilt/Lying to standing	Fall in systolic pressure	120	43	15	12.50
	30 : 15	121	01	21	17.35

B = borderline, Ab = Abnormal, % Ab = percentage of patients with abnormal test result.

TABLE IV: Categorization as per Bellavere criteria.

Category	*Number of patients*
Normal (score 0–1)	71
Early (score 2–3)	35
Definite (score 4–6)	18

TABLE V: Categorization as per Ewing's criteria.

Category	*Number of patients*
Normal	24
Early	11
Definite	00
Severe	20
Not classified as per strict Ewing's criteria but have abnormal test	69

TABLE VI: Categorization (Parasympathetic and Sympathetic dysfunction) as per AFT lab criteria.

Component	*Borderline*	*Abnormal*
Parasympathetic (irrespective of sympathetic status)	21	52
Parasympathetic but no sympathetic abnormality	17	10
Sympathetic (irrespective parasympathetic status)	17	91
Sympathetic but no parasympathetic abnormality	13	49
Sympathetic + parasympathetic	04	42

criteria respectively. Only 53 patients were diagnosed for CAN if Bellavere criteria was used. Using Ewing's criteria, 100 patients were diagnosed as having CAN but 69 patients could not be fitted into the categories as described by Ewing. Using AFT lab criteria 101 patients were found to be having CAN.

The table VII shows genderwise result of each test of autonomic functions (Fig. 1). No differences were found between the males and female patients.

To understand the relationship between autonomic deficit and age, duration of disease and HbA1c of the patient, Pearson's correlation analysis was performed. For each patient, first the score was normalized to the number of tests (total score divided by number of tests) that were performed by that

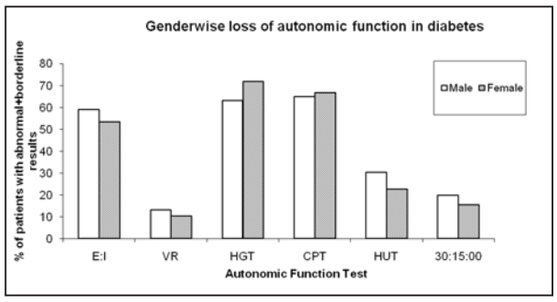

Fig. 1: Gender wise result of each test of autonomic functions.

TABLE VII: Gender wise loss of autonomic function.

Test	*Parameter*	*Male (n=78)*		*Females (n=46)*	
		% Ab	%B	% Ab	%B
Deep breathing test	Delta heart rate	37.17	21.79	22.22	31.11
Valsalva Maneuver	Valsalva ratio	08.70	04.34	03.44	06.89
Handgrip test	Rise in diastolic pressure	39.47	23.68	60.86	10.86
Cold pressor test	Rise in diastolic pressure	47.88	16.90	44.44	22.22
Head up tilt/Lying to standing	Fall in systolic pressure	15.78	14.47	09.09	13.63
	30 : 15	18.42	01.31	15.55	–

%Ab = percentage of patients with abnormal test result. %B = percentage of patients with borderline test result.

patient. The score was kept as dependent variable with age, duration of disease and HbA1c was independent variable (Table VIII, Fig. 2). The autonomic deficit was significantly correlated only with the duration of disease but not with age of the patient or the level of HbA1c.

TABLE VIII: Correlation coefficient and 'P' value of the Pearson's correlation analysis between autonomic score and independent variables (n= 39).

Independent variable	*r*	*P value*
Age	–0.02	0.901
Duration of disease	0.544	0.001
HbA1c	–094	0.570

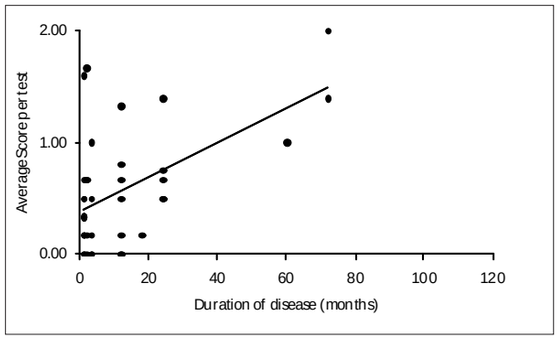

Fig. 2: Scatter plot of Average score and duration of disease.

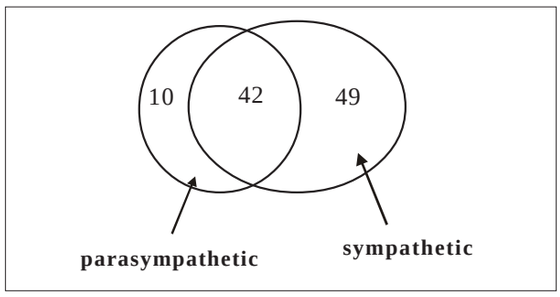

Fig. 3: Venn diagram to show the prevalence of sympathetic and parasympathetic dysfunction in 124 patients.

DISCUSSION

The cardiovascular autonomic status of the diabetic patients referred to autonomic function laboratory, AIIMS was analyzed in the current study. 124 patients of diabetes were referred in 18 months (January 2008 to July 2009) from various clinical departments. The study shows that diabetes affects parasympathetic fibers and sympathetic fibers independently. Hence the tests should be conducted independently for the diagnosing sympathetic and parasympathetic deficits and reported as such. At a tertiary referral centre the prevalence of CAN in diabetics is high (>80%).

The study shows that the autonomic abnormality as assessed on the basis of single test varies from 6.49% in Valsalva ratio to 47.41% in handgrip test. Thus, if only one test is used CAN is likely to be missed. Increase in the number of tests as in Bellavere's criteria led to identification of 53 patients of CAN from 124 patients (42.74%). The Bellavere's criteria uses the heart rate changes in three tests that represent the parasympathetic component. The tests for sympathetic component are not considered in the Bellavere criteria. Ewing's criteria uses the tests for parasympathetic as well as sympathetic component but the sympathetic component is used only for diagnosis of severe CAN. The tests for sympathetic component are not considered for early changes of CAN. As a result when Ewing's criteria are applied, 69 out of 100 patients cannot be classified even though abnormalities were detected in 100 out of 124 patients (80.64%).

San Antonio Consensus Panel had suggested that tests for parasympathetic

and sympathetic should be conducted independently. When analyzed separately, the results show that pure sympathetic abnormality is seen in 49 patients and pure parasympathetic abnormality is seen in only 10 patients while combined abnormalities were seen in 42 patients (Fig. 3). The result suggest that sympathetic abnormality is more common than parasympathetic component and that it is not necessary that parasympathetic dysfunction is followed by the development of sympathetic dysfunction, an assumption that is made by Ewing's criteria as well as by San Antonio Consensus Panel.

Our data suggests that even when the known duration of disease is less, the autonomic dysfunction is likely to be present because the duration of diabetes prior to diagnosis is uncertain and this duration of unknown period may be long due to lack of regular routine check-ups. The longer the duration of diabetes, the more likely is the occurrence of hyperglycemic states even in adequately controlled diabetic. The positive correlation between duration of diabetes type II and autonomic neuropathy has been reported by Philips JC (14) Ninkovic (15), Valensi (16).

The autonomic scores did not correlat significantly either with the age of the patient or with HbA1c. The age of patient at which the diabetes develops and diagnosed is variable. An elderly patient may have diabetes of few months duration while a middle age patient may have diabetes of few years duration. It is the duration of disease rather than the age of patient that is independent risk factor for the development of autonomic dysfunction (17, 18).

The diabetes is caused by hyperglycemia and it is intuitive to accept that sustained hyperglycemia as estimated by HbA1c should correlate with occurrence of diabetic complications like autonomic dysfunction. Long term prospective studies have shown that mean HbA1c over time correlates with severity of the autonomic dysfunction (Larsen 2004(19), Ko. 2008 (20)). These relationship have been established for mean HbA1c in longitudinal studies over 18 years and 7 years rather than a single point HbA1c. A single point HbA1c in a patient under Using Stepwise regression, Pavy-Le Teron et al (21) showed that of scoring of autonomic neuropathy per Ewing's score did not correlate with HbA1c levels of the patient. Other means of assessing severity of diabetes such as HOMA may be better predictors of autonomic dysfunction.

Presence of CAN has been correlated with increase in morbidity and mortality (1). Presence of CAN increases the risk of intra-operative and peri-operative hemodynamic instability (22), intra-operative hypothermia (23), development of orthostatic hypotension and silent myocardial infarction. Given the high incidence of diabetes and high prevalence of CAN, it is recommended that testing for CAN should be done as a routine work-up of diabetic patients. The procedures for performing tests for detection of CAN are safe, non-invasive and require minimal infrastructure.

Limitations of the study

The study was retrospective and data was obtained from the laboratory records. All the patients were referred to AFT laboratory for testing thus the referral bias may overestimate the prevalence.

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REFERENCES

1. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care* 2003; 26(5): 1553–1579.
2. Rolim LC, Sá JR, Chacra AR, Dib SA. Diabetic cardiovascular autonomic neuropathy: risk factors, clinical impact and early diagnosis. *Arq Bras Cardiol* 2008; 90(4): 24–31.
3. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. *Diabetes Care* 2003; 26(6): 1895–1901.
4. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J (Clin Res Ed)* 1982; 285(6346): 916–918.
5. Bellavere F, Bosello G, Fedele D, Cardone C, Ferri M. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J (Clin Res Ed)* 1983; 287(6384): 61.
6. American Diabetes Association. Proceedings of a consensus development conference on standardized measures in diabetic neuropathy. Summary and recommendations. *Diabetes Care* 1992; 15(8): 1104–1107.
7. http://www.who.int/diabetes/facts/world_figures/en/index5.html.
8. Jyotsna VP, Sahoo A, Sreenivas V, Deepak KK. Prevalence and pattern of cardiac autonomic dysfunction in newly detected type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2009; 83(l): 83–88.
9. Bradley JG, Davis KA. Orthostatic hypotension. *Am Fam Physician* 2003; 68(12): 2393–2398.
10. Mathias CJ and Bannister R. Investigation of autonomic disorders. In: Bannister SR and Mathias CJ, editors. Autonomic Failure. A text book of clinical disorders of Autonomic Nervous System. 3rd ed. New York: Oxford University Press; 1992; 253–290.
11. Low PA. Laborotory Evaluation of Autonomic Function. In: Low PA, editor. Clinical Autonomic Disorders. 2nd ed. New York: Lippincott-Raven Publishers; 1997; 179–208.
12. Oribe E and Appenzeller O. Evaluation of autonomic reflexes. In: Mohr JP and Gautier JG, editors. Guide to Clinical Neurology. 1st ed. New York: Churchil Livingstone Inc; 1995; 213–218.
13. Malik M. Clinical Guide to Cardiac Autonomic Tests. Netherlands: Kluwer Academic publishers; 1998.
14. Philips JC, Marchand M, Scheen AJ. Pulse pressure and cardiovascular autonomic neuropathy according to duration of type 1 diabetes. *Diabetes Metab Res Rev* 2009; 25(5): 442–451.
15. Ninković V, Ninković S, Zivojinović D. Cardiovascular autonomous dysfunction in diabetics: the influence of disease duration, glycoregulation degree and diabetes type. *Srp Arh Celok Lek* 2008; 136(9-10): 488–493.
16. Valensi P, Pariès J, Attali JR; Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications–the French multicenter *study. Metabolism* 2003; 52(7): 815–820.
17. Khoharo HK, Ansari S, Ali Shaikh I, Qureshi F. Cardiac autonomic neuropathy (CAN) in type-1 diabetes mellitus patients and its association with the duration of disease and glycemic control. *J Coll Physicians Surg Pak* 2009; 19(4): 232–235.
18. Hsu WC, Yen AM, Liou HH, Wang HC, Chen TH. Prevalence and risk factors of somatic and autonomic neuropathy in prediabetic and diabetic patients. *Neuroepidemiology* 2009; 33(4): 344–349.
19. Larsen JR, Sjøholm H, Berg TJ, Sandvik L, Brekke M, Hanssen KF, Dahl-J0rgensen K. Eighteen years of fair glycemic control preserves cardiac autonomic function in type 1 diabetes. *Diabetes Care* 2004; 27(4): 963–966.
20. Ko SH, Park SA, Cho JH, Song KH, Yoon KH, Cha BY, Son HY, Yoo KD, Moon KW, Park YM, Ahn YB. Progression of cardiovascular autonomic dysfunction in patients with type 2 diabetes: a 7-year follow-up study. *Diabetes Care* 2008; 25(10): 1171–1177.
21. Pavy-Le Traon A, Fontaine S, Tap G, Guidolin B, Senard JM, Hanaire H.Cardiovascular autonomic neuropathy and other complications in type 1 diabetes. *Clin Auton Res* 2010; 20(3): 153–160.
22. Burgos LG, Ebert TJ, Asiddao C, Turner LA, Pattison CZ, Wang-Cheng R, Kampine JP. Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. *Anesthesiology* 1989 Apr; 70(4): 591–597.
23. Kitamura A, Hoshino T, Kon T, Ogawa R. Patients with diabetic neuropathy are at risk of a greater intraoperative reduction in core temperature. *Anesthesiology* 2000 May; 92(5): 1311–1318.