Assessment of cardiovascular autonomic function in the anaesthesia population

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Chapter 2

The impact of autonomic dysfunction on perioperative cardiovascular complications

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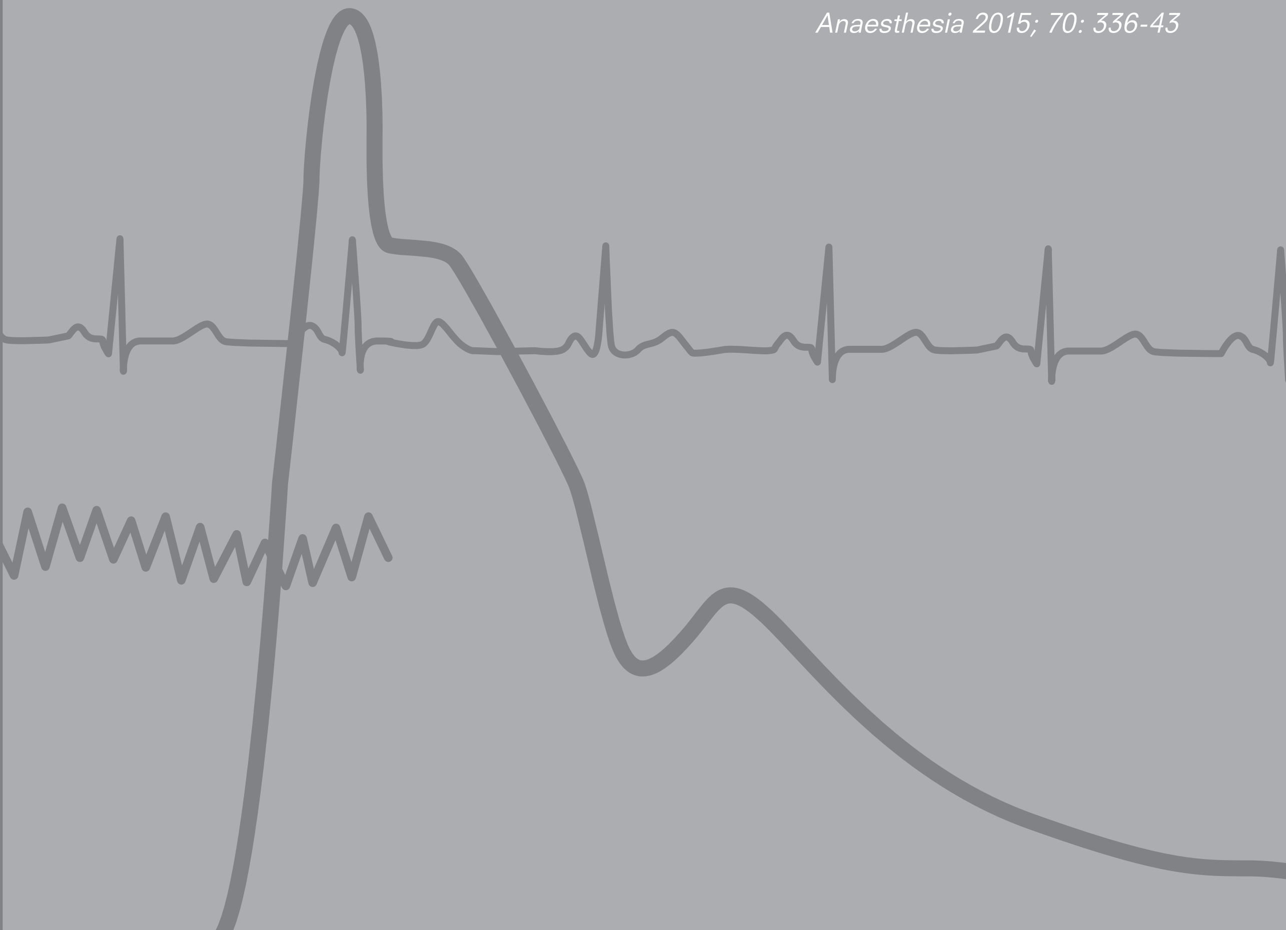


ABSTRACT

Cardiovascular autonomic neuropathy is frequently observed in patients with diabetes mellitus. Since anaesthesia has a marked effect on perioperative autonomic function, the interplay between diabetic neuropathy and anaesthesia may result in unexpected haemodynamic instability during surgery. The objective of this literature review was to examine the association of cardiovascular autonomic neuropathy with perioperative cardiovascular complications. We searched Pubmed for articles with search elements of autonomic dysfunction [MESH] AND anaesthesia [MESH] AND complications [MESH]. Depending on the type of anaesthesia, the presence of cardiovascular autonomic neuropathy in surgical patients can markedly affect perioperative haemodynamics and postoperative recovery. Preoperative testing of the extent of autonomic dysfunction in particular populations, like diabetics, may contribute to a reduction in haemodynamic instability and cardiovascular complications. Non-invasive diagnostic methods assessing autonomic function may be an important tool during preoperative risk assessment.

INTRODUCTION

Autonomic dysfunction is a broad term that describes any disease or malfunctioning of the autonomic nervous system. It may also involve the cardiovascular system, in which case it is known as cardiovascular autonomic neuropathy [1]. Diabetes mellitus is one of the most overlooked morbidities in surgical patients. It can cause damage to the autonomic nerve fibres that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics [2-5]. Diabetes mellitus is one of the most common neuropathic disorders, and 20-40% of all diabetic patients show abnormal autonomic function [2, 6-7]. The presence of cardiovascular autonomic neuropathy is predictive for perioperative haemodynamic instability and postoperative complications [5, 7-10].

Since anaesthesia is a major influence on perioperative autonomic function, the interplay between cardiovascular autonomic neuropathy and anaesthesia may result in unexpected haemodynamic instability during surgery [5, 7-12]. Indeed, it has been shown that diabetic patients with autonomic neuropathy are prone to develop more cardiovascular events, including bradycardia, hypotension and cardiopulmonary arrest during induction of anaesthesia compared with non-diabetic subjects [2, 7]. In particular, perioperative cardiovascular morbidity and mortality are increased two- to threefold in patients with diabetes mellitus [2, 13].

Previous studies examining the association of cardiovascular autonomic dysfunction and mortality reported a significant higher mortality rate among diabetics with cardiovascular autonomic neuropathy compared with diabetic patients without it [5-6, 13-14]. The variability of mortality rates revealed in these studies may be related to the chosen study population, the heterogeneous methodology for assessing cardiovascular autonomic dysfunction and the criteria used to define its presence.

It is estimated that 50% of diabetic patients will require some type of surgical procedure in their lifetime [7]. In addition, one-third of all postoperative complications are due to cardiac complications, which has important implications for the anaesthetist [7]. Therefore, the objective of the present literature study was to provide a descriptive review, for perioperative physicians, of studies describing the impact of autonomic dysfunction on perioperative cardiovascular complications. We particularly aimed to investigate the association between autonomic dysfunction and the increased risk of cardiovascular complications by pooling results across published articles.

METHODS

We searched Pubmed in June 2014 for articles with the keywords autonomic dysfunction AND anaesthesia AND complications (all MESH-terms); this resulted in a total of 441 articles. After limiting the research results to English, humans, clinical trials, meta-analysis, practice guidelines, reviews and randomised controlled trials, 93 articles remained. From this subset, 40 articles focusing on cardiovascular complications (like myocardial infarction, heart failure, ventricular and atrial fibrillation, bradycardia, hypotension, angina, need for coronary revascularisation or risk of sudden cardiac death/cardiopulmonary arrest) were selected for this literature survey. The other 53 articles had another focus (such as sepsis, traumatic brain injury, et cetera) and were excluded. Furthermore, we included other relevant articles, which were found in the reference list of the 40 remaining articles, giving us a total of 49 articles for inclusion.

RESULTS
Epidemiology of autonomic neuropathy

Many diseases, such as autoimmune, endocrine, or degenerative disorders, and many conditions, such as trauma, or paraneoplastic syndromes, can cause cardiovascular autonomic neuropathy. It can also be a side effect of treatment such as chemotherapy or radiation. However, almost all articles that were found by this search dealt purely with diabetes mellitus, which is one of the most common neuropathic disorders and the most relevant [2].

Cardiovascular autonomic neuropathy develops slowly over a number of years [15]. However, in published studies, prevalence rates between 1% and 90% are reported due to the use of a variety of study endpoints [2]. This is further complicated by the differences in the methodology used and the lack of standardisation with respect to diagnosis. Therefore, standardisation of the diagnosis is necessary so that the true prevalence can be determined, and this is not yet clear from the literature.

Diagnosis of autonomic neuropathy

A number of studies have evaluated autonomic function in patients with diabetes mellitus based on heart rate variability [16-17]. Abnormalities in heart rate variability may be indicative of the early stage of cardiovascular autonomic neuropathy, whereas resting tachycardia and a fixed heart rate are later characteristics in diabetic patients. During exercise, autonomic dysfunction is characterised by impaired exercise tolerance, a reduced response of heart rate and blood pressure, and a blunted increase in cardiac output [2].

Heart rate variability measured at rest is a simple approach to recognise autonomic dysfunction and can be measured over five minutes (short-term) or during a 24-hour period of monitoring (long-term). To evaluate cardiovascular autonomic function, different heart rate variability frequency bands are determined. Sympathetic function is mainly represented in the very low frequency band (0.00–0.04 Hz), which is related to fluctuations in vasomotor tone and is associated with thermoregulation, whereas the high frequency band (0.12–0.40 Hz) may represent the efferent vagal activity and is related to respiratory activity. The low frequency band (0.04–0.12 Hz) may be a representative of parasympathetic as well as sympathetic innervation, and is associated with the baroreceptor reflex (Table 1) [2, 18-22].

Heart rate variability over a five-minute period at rest in the supine position can be used, but its application in research and clinical practice remains a topic of discussion [20, 22-24]. For the very low frequency band, a recording of five minutes may be to short [20]. However, five minutes seems to be adequate for the low and high frequency band [20].

Other parasympathetic function batteries of tests include heart rate response during deep breathing, the Valsalva manoeuvre, and standing up quickly. Sympathetic function tests include blood pressure response during a sustained handgrip, and standing quickly [19, 21, 25]. There are only a limited number of reports detailing reference values for cardiovascular autonomic function tests in healthy subjects [19-21, 22-25]. During deep breathing, the maximum and minimum R-R intervals during each breathing cycle are measured: six breathing cycles of five seconds of inspiration and five seconds of expiration during one minute. The R-R interval during inspiration and expiration is determined and expressed as a ratio. In normal healthy subjects the average ratio between the R-R during expiration and inspiration is greater than 1.17. In addition, a Valsalva manoeuvre can be performed by blowing into a manometer (40 mmHg) for 15 seconds. The Valsalva ratio is defined as the ratio between the longest time between two consecutive R-waves of the ECG (R-R interval) and the shortest, measured immediately after the Valsalva manoeuvre. The average value of three measurements should be greater than 1.21. After standing up quickly, the R-R intervals at 15 and 30 beats are measured. In healthy subjects, the ratio of the longest R-R interval to the shortest should be greater than 1.04 [19, 21, 25].

Table 1.
Frequency bands reflecting autonomic innervation in heart and pulse rate variability.

Variability	Frequency	Autonomic nervous system
HR or PR	VLF (< 0.04 Hz); ms^2	Sympathetic
HR or PR	LF (0.04-0.12 Hz); ms^2	Both
HR or PR	HF (0.12-0.40 Hz); ms^2	Parasympathetic

HR, heart rate; PR, pulse rate; VLF, very low frequency; LF, low frequency; HF, high frequency.

Table 2.
Reference values for cardiovascular autonomic function tests.

Test		Ratio	Autonomic nervous system
Deep breathing; HR response	Longest R-R / shortest R-R	> 1.17	Parasympathetic
Valsalva manoeuvre; HR response	Longest R-R / shortest R-R	> 1.21	Parasympathetic
Quick-standing; HR response	Longest R-R / shortest R-R	> 1.04	Parasympathetic
Sustained handgrip; BP response	Raising of diastolic blood pressure	> 16 mmHg	Sympathetic
Quick-standing; BP response	Fall in systolic blood pressure	< 10 mmHg	Sympathetic

HR, heart rate; BP, blood pressure; R-R, R-R interval.

For sympathetic function, a sustained handgrip (30% of maximum contraction using a handgrip dynamometer for five minutes) should lead to an increase in diastolic blood pressure by more than 16 mmHg in the opposite arm in healthy subjects. During the quick-standing (Schellong) test, systolic blood pressure is first measured in the supine resting state. Two minutes after standing up quickly, the systolic blood pressure is measured again. In normal healthy subjects, the drop in systolic blood pressure is less than 10 mmHg [6, 18, 21, 25-26]. A fall in systolic pressure of 20 mmHg or more indicates impaired cardiovascular autonomic circulatory function (Table 2).

In addition, a new test has been developed, which is based on the measurement of sweat production after exposure to dermal foot perspiration [27]. Furthermore, prolongation of the corrected QT interval (QTc) in the electrocardiogram seems to be a specific indicator of cardiovascular autonomic neuropathy in most studies, and may be predictive for sudden cardiac death in type I and II diabetic patients [15].

Cardiovascular complications

The relationship between cardiovascular autonomic neuropathy and cardiovascular events during and after surgery has been assessed in a number of studies. These cardiovascular events include: myocardial infarction; heart failure; ventricular and atrial fibrillation; angina; need for coronary revascularisation; and risk of sudden cardiac death [2, 15]. Generally, the risk of cardiovascular complications is the highest among patients with previous myocardial infarction, angina pectoris, congestive heart failure, and diabetes mellitus [28]. Among patients undergoing vascular surgery without other cardiovascular comorbidities, the combined incidence of perioperative myocardial infarction or death is approximately 3% [28]. In patients with three or more cardiovascular comorbidities, the risk of cardiac failure is between 15 and 20% [28]. Studies in patients undergoing vascular surgery have shown that a non-fatal myocardial infarction in the early postoperative period confers a four-fold increase in the risk of a fatal or non-fatal myocardial infarction following four years after surgery [28]. In addition to cardiovascular autonomic neuropathy associated with diabetes mellitus, there are many other diseases which can lead to cardiovascular autonomic neuropathy. For example, patients with familial amyloid polyneuropathy may also have progressive autonomic neuropathy. This disease is associated with sudden death, conduction disturbances and an increased risk of complications during anaesthesia

[29]. Furthermore, alteration of the autonomic nervous system has also been described in heart failure. Sánchez-Lázaro et al. concluded that in stable patients with advanced heart failure, both sympathetic and parasympathetic autonomic nervous systems can be affected [30]. Therefore, as the presence of cardiovascular autonomic neuropathy may have profound effects and complicate postoperative recovery, its diagnosis is essential as part of the assessment of risk.

Effect of anaesthesia

Different anaesthetic agents and techniques may have different effects on patients with autonomic neuropathy. Hanss et al. showed that xenon anaesthesia, in contrast with propofol and remifentanil, did not produce haemodynamic depression during surgery, and that it increased parasympathetic and decreased sympathetic activity [31]. Its use may be beneficial in patients at high risk of intraoperative haemodynamic instability and perioperative cardiac complications [31]. However, due to costs and technical aspects, the use of xenon anaesthesia is limited.

Anaesthesia in combination with analgesia is of benefit for cardiovascular autonomic neuropathy patients. After balanced anaesthesia with, for example, remifentanil, more pronounced sympatho-adrenergic stimulation occurs because of the more rapid clearance of the analgesic effect in the recovery period compared to alfentanil [32]. This is further associated with a decreased requirement of additional medication for the control of haemodynamic parameters as showed by Apitsch et al. [32]. Moreover, midodrine, an alpha-1 adrenergic agonist, is known to increase blood pressure and total peripheral resistance. It also limits the decrease in arterial pressure observed during exercise in patients with autonomic dysfunction [33].

An important result of the study of Adams et al. included that neurolepto-anaesthesia leads to better stress protection in the postoperative period while isoflurane anaesthesia has some advantages for the intraoperative control of arterial pressure [34]. Vohra et al. compared cardiovascular responses to the induction of anaesthesia and to tracheal intubation after propofol and pancuronium in both diabetic and non-diabetic patients [35]. Heart rate and cardiac index increased in the control group, while in the diabetic group, heart rate remained unaltered and cardiac index decreased. In another study, the duration of parasympathetic impairment was compared after the use of two anticholinergic drugs, atropine and glycopyrrolate. Both agents suppress parasympathetic control in the early postoperative period, and impaired parasympathetic control of heart rate is associated with increased incidence of cardiac arrhythmias and ischemia [36]. Parlow et al. concluded that atropine leads to a more prolonged impairment of parasympathetic control than glycopyrrolate, and its use may thus be less desirable in high-risk patients with autonomic function disturbances [36].

It is vital to evaluate heart rhythm as reflected by the number of P-waves per QRS complex, the configuration of the QRS and any arrhythmias. It has been shown that precise evaluation and management of perioperative arrhythmias may reduce anaesthetic morbidity and mortality [37]. Patients who develop ventricular tachycardia had significantly more atrial premature contractions, ventricular premature contractions and postoperative atrial fibrillation, 34% versus 17%, than those without ventricular tachycardia. The authors concluded that non-sustained ventricular tachycardia after non-cardiac surgery occurs frequently but is not associated with poor outcome [38].

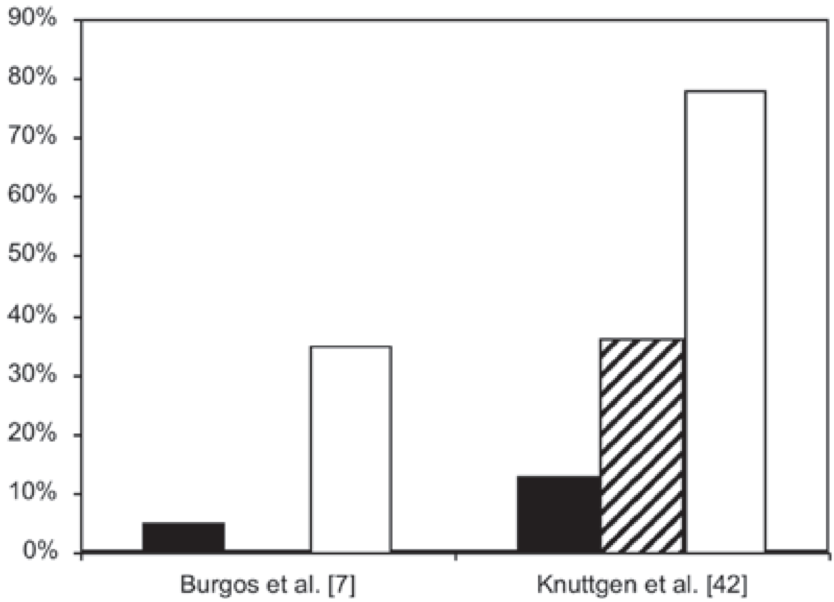
Effects of regional anaesthesia

Studies focused on the effects of regional anaesthesia on autonomic function are limited. Breslow et al. showed in adults undergoing surgery on the abdominal aorta, in a randomised, double blind, placebo-controlled study, that epidural morphine decreased postoperative hypertension by attenuating sympathetic nervous system hyperactivity [39]. In non-diabetic patients following lung resection surgery, heart rate variability and baroreflexes were markedly decreased in both the patient-controlled analgesia as well as the thoracic epidural analgesia group. However, these parameters recovered better in the thoracic epidural analgesia group, which may be an important finding for patients with autonomic dysfunction [40]. Nevertheless, thoracic epidural analgesia has no effect on the incidence of postoperative sustained atrial fibrillation, despite a significant reduction in sympathetic activity [41].

Preoperative assessment

As mentioned previously, diabetes mellitus is associated with a two- to threefold risk for perioperative cardiovascular morbidity and mortality [2, 13]. In comparison with non-diabetic subjects, diabetic patients undergoing general anaesthesia may experience a greater decline in heart rate and blood pressure during induction of anaesthesia. In addition, patients with severe autonomic dysfunction have a high risk of blood pressure instability, and intraoperative blood pressure support is needed more often in those with greater autonomic impairment (Figure 1) [2, 7].

Figure 1.
Studies of Burgos et al. [7] and Knüttgen et al. [42]. Percentages of patients who are non-diabetics (■), diabetics without impaired autonomic function (◩) and diabetics with impaired autonomic function (□), who required vasopressors for intraoperative hypotension during ophthalmic surgery under general anaesthesia.



Knüttgen et al. demonstrated that there was a significant relationship between preoperative heart rate variability at rest and cardiovascular stability during induction of anaesthesia in diabetic patients (Figure 1) [42]. Earlier studies from the same group also demonstrated that haemodynamic stability in the perioperative period depends on the severity of the autonomic dysfunction, and that diabetics with severe autonomic neuropathy have a greater risk of cardiovascular instability [8]. They also found a moderate correlation between the degree of autonomic dysfunction and the greatest drop in blood pressure under anaesthesia [9].

A few studies have shown that decreased heart rate variability preoperatively can independently predict long-term postoperative mortality [43-44]. Intraoperative hypothermia and an impaired hypoxia-induced ventilation drive have also been shown to be associated with the presence of cardiovascular autonomic neuropathy. Fifteen studies have included follow-up for mortality, where total mortality rates were higher in subjects with cardiovascular autonomic neuropathy at baseline than in those whose baseline assessment was normal, with statistically significant differences in eleven of these studies [43-44].

Linstedt et al. also tested patients preoperatively for autonomic cardiovascular dysfunction, and showed increased variability of systolic blood pressure compared to non-diabetics [10]. This might be related to autonomic dysfunction, caused by the hypersensitivity of partly damaged autonomic nervous fibres, or impaired haemodynamic control. Eventually, this impairment led to the loss of heart rate variability and vascular tone [10]. The retrospective study of Goto et al. also included preoperative measurements, but in this study the level of fructosamine was determined [45]. They concluded that fructosamine might predict intraoperative risk in diabetes patients during anaesthesia, leading to a possible relationship between fructosamine and autonomic nerve function [45].

Preoperative testing of diabetic patients is crucial to determine the level of autonomic dysfunction, and the risk of perioperative cardiovascular complications and haemodynamic instability, that may lead to sudden cardiac death. Further studies in surgical patients are needed to establish a possible predictive value of preoperative baroreceptor dysfunction, alone and combined with heart rate variability, for short- and long-term postoperative outcome.

Perioperative autonomic testing in the future

Anaesthesia affects the integrity of the autonomic nervous system, and anaesthetists therefore use vital signs to maintain respiratory and circulatory homeostasis. The development of methods to measure autonomic function in the preoperative period could be of interest to anaesthetists, since they may allow the detection of changes in autonomic function before vital signs are affected. New non-invasive methods are being developed to obtain measurements of parasympathetic and sympathetic control [18, 19, 21, 46].

Preoperative screening of diabetics with simple non-invasive autonomic tests may be useful in identifying those at high risk for perioperative cardiovascular instability [5]. A major finding of Burgos et al. was that diabetics who required intraoperative blood pressure support had significantly greater impairment of autonomic test results compared with those diabetics who did not need vasopressors [7]. We recently showed that the reproducibility of most autonomic tests under non-standardised conditions is acceptable, and propose the implementation of these tests during preoperative assessment [19, 21].

Although perioperative treatment guidelines for most neurologic disorders have not been reported to reduce morbidity, knowledge of the clinical features and the interaction of common anaesthetics with drug therapy is important in planning management [47]. Screening for autonomic neuropathy may therefore be helpful to improve the management of patients with diabetes who undergo surgery requiring general anaesthesia [48-49].

CONCLUSION

Inclusion of autonomic function testing in the preoperative period may contribute to improved intraoperative safety and may result in the development of tailor-made anaesthesia for patients with autonomic function disturbances [18, 19, 21, 49]. Cardiac complications in patients undergoing non-cardiac surgery account for 40% of perioperative mortality [49]. Among others, the most important cardiac complications of surgery are cardiac death, myocardial ischemia or infarction, cardiac arrest, and pulmonary oedema. General anaesthesia results in an increased activation of the sympathetic nervous system, which may lead to anaemia, hypoxia, infection, and reduced or excess blood volume. These complications frequently cause postoperative tachycardia and hypertension, which increases myocardial oxygen demand and may lead to unstable angina, myocardial infarction, or arrhythmias in the presence of ischaemic heart disease.

Despite the fact that cardiovascular disease is common, cardiac morbidity and mortality from surgery is low. However, patients undergoing major surgery or vascular surgery frequently suffer from cardiovascular comorbidities like diabetes mellitus, and are therefore prone to intravascular risks. In particular, diabetic subjects frequently show abnormal autonomic function caused by autonomic neuropathy. In addition, the incidence of cardiovascular events during the perioperative period increases with advancing age, urgency and type of surgery.

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