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Assessment of cardiovascular autonomic function in the anaesthesia population

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2015

document version
Publisher's PDF, also known as Version of record

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citation for published version (APA)
Keet, S. W. M. (2015). *Assessment of cardiovascular autonomic function in the anaesthesia population.*

Chapter 1

General introduction
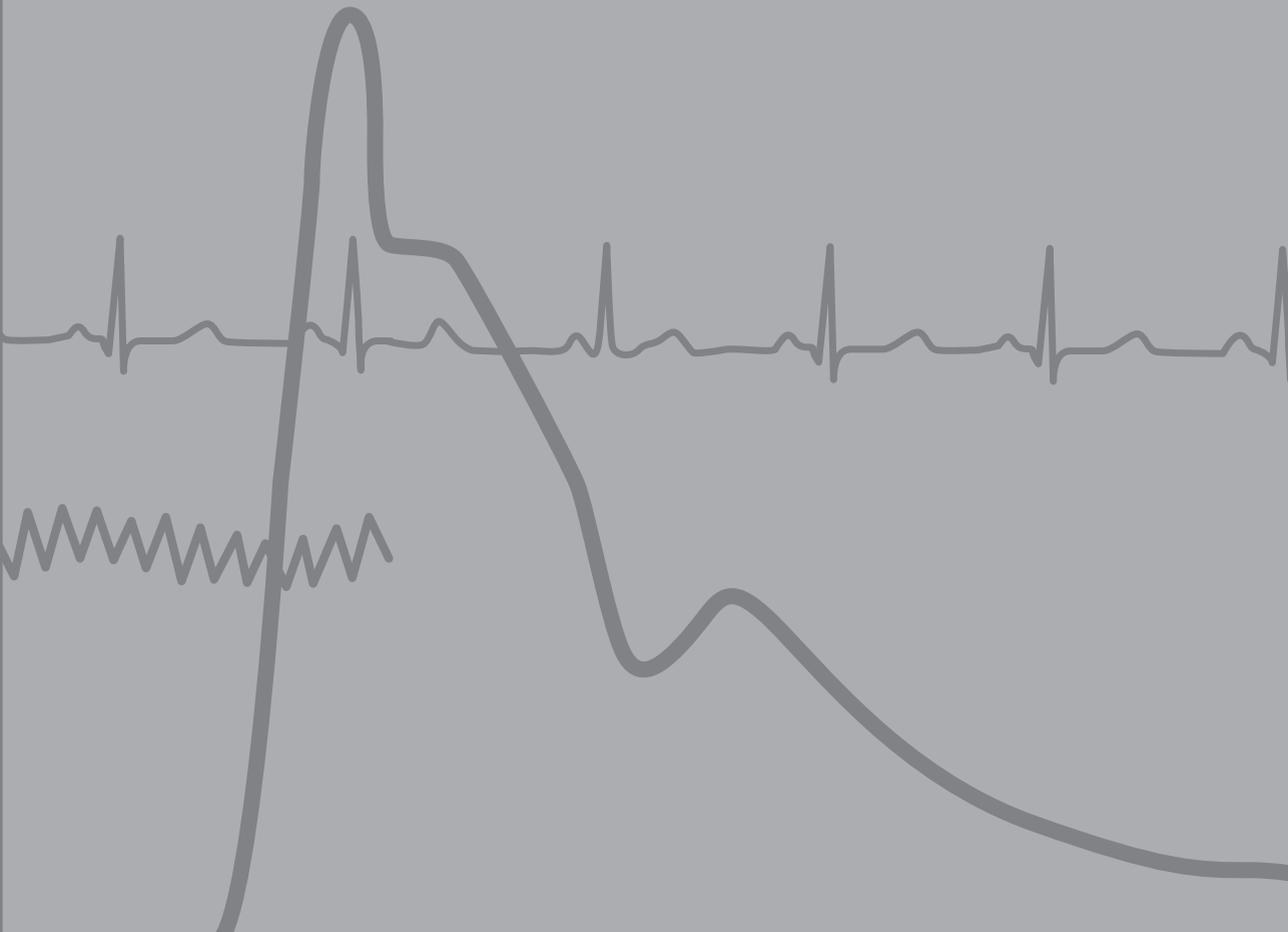
The autonomic nervous system

The autonomic nervous system regulates unconscious body functions to maintain homeostasis, including blood pressure regulation, heart rate, the function of the stomach and intestines and the rate of respiration [1-6]. The sensory part of the autonomic nervous system is involved in senses like taste, seeing, hearing and pain [1-6]. The motor part of the autonomic nervous system can be divided into the sympathetic and parasympathetic nervous system [1-6]. While the sympathetic part of the autonomic nervous system is mostly associated with activation of organ function, the parasympathetic part is associated with dampening of organ function [1-6].

Most human organs are innervated by the parasympathetic as well as the sympathetic nervous system. The distinct functions of the parasympathetic and sympathetic system are shown in Table 1 [1-6].

It is important to understand the interactions of the parasympathetic and the sympathetic function, for instance to predict the effects of anaesthetics influencing the autonomic nervous system [5]. A sympathetic blockade may unmask pre-existing parasympathetic activity and a parasympathetic blockade may unmask pre-existing sympathetic activity. For example, a parasympathetic blockade may lead to a tachycardia and/or an increase in blood pressure due to the sympathetic drive [5].

Table 1.
Organ function regulated by the sympathetic and parasympathetic system.

Sympathetic system	Parasympathetic system
Increase in heart rate	Decrease in heart rate
Increase in blood pressure	Decrease in blood pressure
Increase in blood glucose concentration	Reduction of blood glucose concentration
Increase in muscular blood flow	Reduction of muscular blood flow
Dilation of pulmonary bronchioles	Constriction of pulmonary bronchioles
Pupil dilation	Pupil constriction
Reduction in intestinal function	Increase in intestinal function

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**The sympathetic nervous system; "fight or flight"**
Sympathetic nerve fibres originate from thoracic and lumbar regions of the spinal cord and involve preganglionic and postganglionic neurons. Preganglionic neurons release acetylcholine to activate postganglionic neurons, which in most cases subsequently release acetylcholine or noradrenalin to activate the adrenergic receptors. Moreover, through acetylcholine release in the adrenal medulla, the sympathetic nervous system influences the regulation of vascular smooth muscle through the release of adrenaline and noradrenaline. Preganglionic neurons are shorter than postganglionic neurons in the sympathetic nervous system [1-6]. Figure 1 shows a diagram of the anatomical organisation of the autonomic nervous system.

The sympathetic nervous system influences many functions of the body but the effects on respiration and circulation are the most important [5]. The adrenergic system facilitates "fight or flight" [1-6]. The cardiac output and ventilation increases whereas the function of the gastrointestinal tract decreases when the adrenergic system is stimulated [1-6]. Nevertheless, the stress response may differ in appearance and intensity [1-6].

The parasympathetic nervous system; "vegetative processes"
Parasympathetic nerve fibres arise from the brainstem and sacral region of the spinal cord, and act through the activation of nicotinic preganglionic and muscarinic postganglionic receptors (Figure 1). Preganglionic neurons are longer than postganglionic neurons in the parasympathetic nervous system. Parasympathetic function can be divided into three areas: the cranial nerves, the vagus nerve and the pelvic splanchnic nerves. With respect to regulation of the cardiovascular system, the vagus nerve plays a central role in the regulation of heart rhythm, as its stimulation leads to lowering of the heart rate, and overstimulation may lead to bradycardia [1-6]. The parasympathetic or cholinergic nervous system tends to be responsible for conserving energy and the stimulation of the vegetative processes [1-6].

Figure 1.
Simplified diagram of the anatomical organisation of the autonomic nervous system.
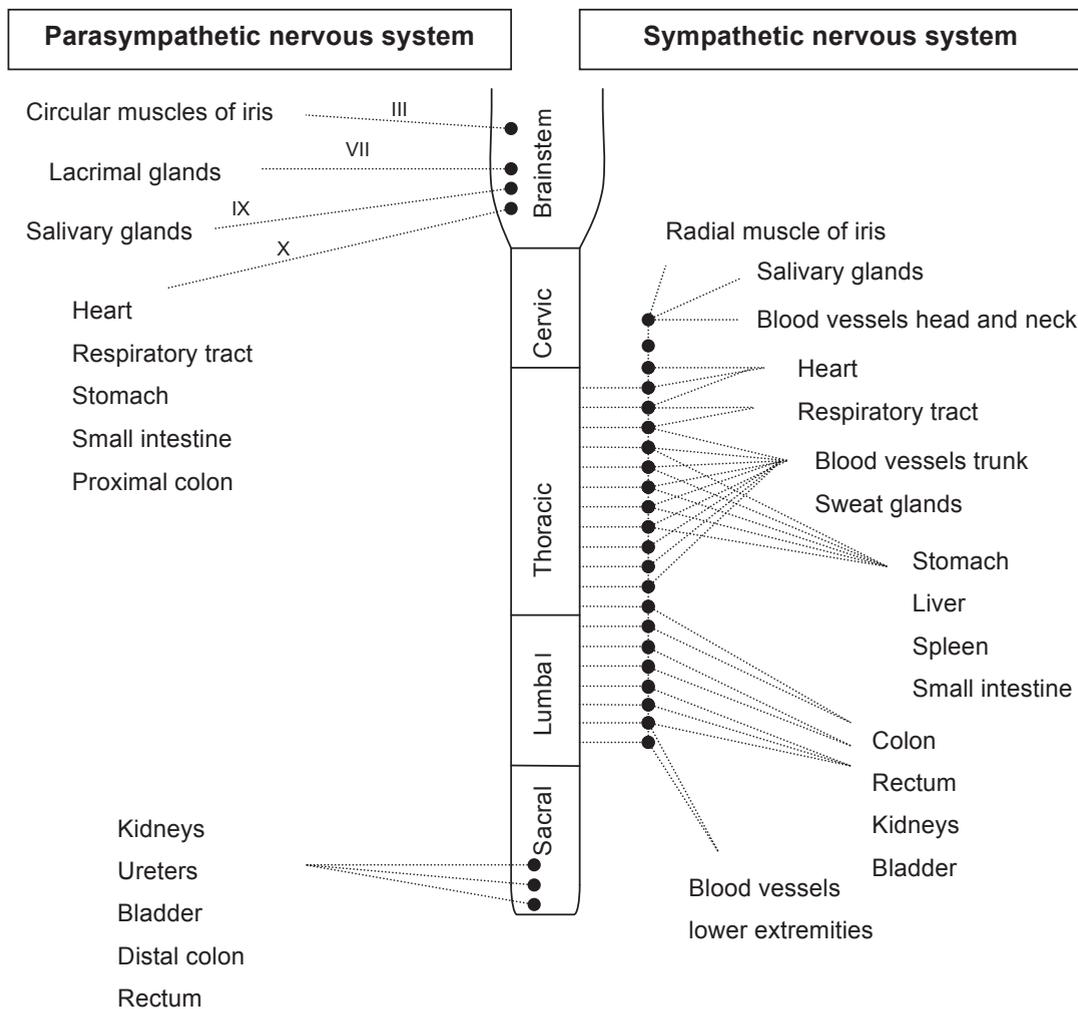
Autonomic dysfunction

Pathological processes that have an impact on the central as well as the peripheral nervous system may result in disorders of the autonomic nervous system [1-6]. Many diseases and disorders, such as endocrine or degenerative disorders, may cause autonomic neuropathy [1-7]. Cardiovascular diseases like heart failure and diabetes mellitus are frequently complicated by impaired cardiovascular autonomic innervation and, in later stages as disease progresses, cardiovascular autonomic neuropathy [7-8]. In heart failure patients, the sympathetic and parasympathetic nervous systems are in imbalance, with an increased sympathetic drive and withdrawal of vagal nerve activity [9]. The excessive release of noradrenaline and impaired vagal function in heart failure patients leads to a higher heart rate and contributes to myocardial remodelling and failure [9].

Autonomic dysfunction during diabetes mellitus is grossly caused by metabolic derangements, including insulin insensitivity, hyperinsulinaemia and hyperglycaemia [3, 6, 10]. Diabetes mellitus is one of the most common causes of neuropathic disorders in perioperative patients, and anaesthetists should therefore be aware of autonomic dysfunction in patients with disturbances in glucose metabolism [7, 11-13].

The pathogenesis of diabetic autonomic dysfunction

The UK Prospective Diabetes Study [14] and Diabetes Control and Complications Trial [15], both multicentre randomised controlled trials, showed that intensive blood-glucose control decreases microvascular complications and, as a result, slows the progression of autonomic neuropathy [10, 14-15]. Although alterations in blood glucose levels in diabetic patients promote the development of autonomic dysfunction, the inter-patient differences between level of blood glucose and microvascular complications are large [10, 14-15]. Therefore, it is likely that the pathogenesis of autonomic neuropathy in diabetic subjects involves different pathways in addition to disturbed glucose control [10].

Microangiopathy as observed during diabetes mellitus is caused by the excessive intake of glucose by the vascular endothelium, leading to increased surficial glycoprotein expression, basement membrane thickening and loss of vascular integrity [16-17]. This may lead to a reduction

in vascular regulation, local hypoxia, and neuronal damage.

In addition to microangiopathy, high glucose levels directly affect nerve fibres, leading to neurological disorders that may consequently impair vascular and cardiac function [1, 6, 16-17].

The most important factors that may contribute to the development of autonomic dysfunction in patients with diabetes are Advanced Glycation End products (AGEs), the Protein kinase C (PKC) pathway and the concept of intracellular hyperglycaemia [6, 10, 16-17].

Advanced glycation end products are a result of the glycation of proteins by the addition of a carbohydrate that consequently leads to irreversible degeneration of the proteins. During hyperglycaemia, more AGEs are formed than under normoglycaemic conditions. It is well known that AGEs contribute to the development of diabetes mellitus, atherosclerosis and renal failure, as they enhance oxidative damage to cells. Due to protein degeneration, AGE formation may additionally lead to microangiopathy [6, 8-10].

A second pathway involves the activation of intracellular protein kinase C through intracellular hyperglycaemia. Activation of PKC may lead to neovascularisation, deposition of basement membrane material and extracellular matrix, reduced fibrinolysis, and may therefore lead to microangiopathy as well [6, 10, 16-17].

The third component that promotes microangiopathy and diabetic autonomic neuropathy is the development of intracellular hyperglycaemia. Unused glucose can be reduced to sorbitol and subsequently fructose. Under normal circumstances, fructose is phosphorylated to form fructose-6-phosphate, which enters the glycolysis pathway. However, with hyperglycaemia, there is more delivery of fructose than the glycolysis pathway can process, leading to accumulation of sorbitol. Since sorbitol cannot cross the cell membrane, its accumulation leads to osmotic stress, influx of water and osmotic cell injury [6, 10, 16-17].

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Figure 2.
Diabetic autonomic dysfunction is caused by direct neurological injury, leading to necrosis, hypoxia and apoptosis of nerve fibres, hyperglycaemia-associated activation or production of advanced glycation end products, protein kinase C and intracellular sorbitol, and reduced nervous blood flow due to microvascular dysfunction and endothelial injury.
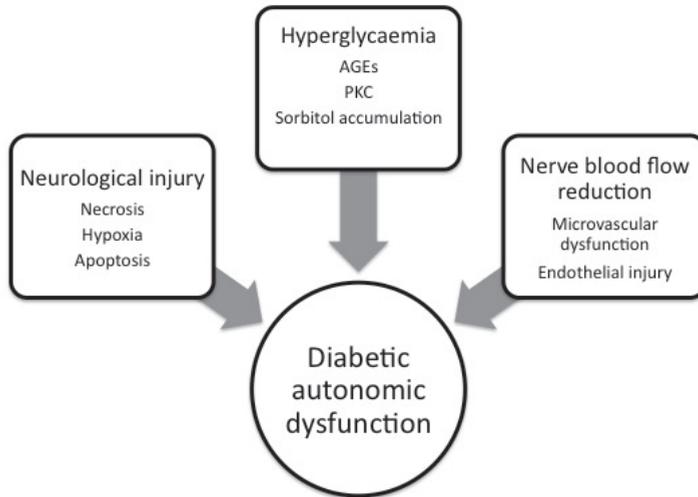
The impact of autonomic dysfunction on patient health

Advanced age and the presence of health risk factors such as obesity and smoking are particularly associated with the development of cardiovascular diseases, and on that account to more perioperative complications [7, 18-22]. Cardiovascular risk factors and concomitant diseases may lead to prolonged hospital stay, delayed patient recovery and deterioration of postoperative health which implies a high financial and societal impact [7, 18-22].

An often unnoticed pathophysiological factor that is linked to cardiovascular disease is cardiovascular autonomic neuropathy [11]. On the one hand, autonomic neuropathy might in itself lead to the development of cardiovascular disease [11]. On the other hand, several cardiovascular diseases, including renal dysfunction and heart failure, may be complicated by the progression of autonomic dysfunction [1, 11]. The presence of cardiovascular autonomic neuropathy may contribute to an increased risk of perioperative complications, since anaesthesia directly influences autonomic function [5, 7, 11-13, 23-30]. Consequently, diabetic patients with autonomic neuropathy show a higher perioperative cardiovascular morbidity compared with non-diabetic subjects [7, 11, 25-26].

Assessment of cardiovascular autonomic function

Routine preoperative assessment to evaluate the integrity of cardiovascular autonomic function may therefore be of added value for perioperative cardiovascular risk prediction and management [7-8, 31]. Traditionally, the diagnosis of autonomic dysfunction requires a battery of tests for parasympathetic and sympathetic function [7, 11, 32-34]. These tests include classical Ewing tests and quantitative assessment of beat-to-beat heart rate variability [7, 11, 32-34].

Classical Ewing tests are based on heart rate and blood pressure responses to different procedures such as controlled breathing or quick standing [7, 11, 32-34]. Heart rate variability comprises evaluation of consecutive R-R intervals during 5 minutes up to 24 hours [35]. A more regular and/or higher heart rhythm leads to lower heart rate variability. A decline in heart rate variability is an indicator of impaired autonomic function [35]. Even mental strain, which leads to a higher heart rate, dampens the heart rate variability. The different parameters of heart rate variability are presented in time domain or frequency domain values [7, 35].

This battery of tests is however difficult to enrol in the routine preoperative setting due to the requirement of a standardised test environment, and the time required for the tests. Furthermore, implementation of these tests in this setting is more complicated since international guidelines recommend standardised test conditions, including refraining from smoking, eating and drinking [32]. Since the presence of autonomic dysfunction may be used as a predictor of cardiovascular events in the perioperative setting, and may therefore contribute to a reduction in perioperative complications, the development of a simplified autonomic test algorithm under non-standardised conditions is warranted [7, 12-13, 25-28, 35-37].

Aim and outline of this thesis

The central hypothesis of the thesis is that simple preoperative cardiovascular autonomic function tests during non-standardised test conditions, with specific emphasis on heart and pulse rate variability, are a valuable tool to identify patients at risk of perioperative cardiovascular complications. Since cardiovascular autonomic neuropathy in surgical patients can markedly affect perioperative haemodynamics and postop-

erative recovery, the addition of preoperative autonomic function testing may contribute to the recognition of patients at risk for postoperative complications.

In **Chapter 2** we reviewed the latest evidence about the association of cardiovascular autonomic neuropathy with perioperative cardiovascular complications.

In **Chapter 3** we investigated the prevalence of lifestyle risk factors in patients admitted to the preoperative assessment outpatient clinic, and compared patient self-reports and anaesthetist reports of health risk factors to evaluate the patient self-image of preoperative health status.

Pulse rate variability is less influenced by environmental factors and may provide a feasible alternative for heart rate variability in the surgical setting. In **Chapter 4** we aimed to investigate the level of agreement between pulse rate variability and traditional heart rate variability for determination of autonomic function in healthy subjects.

In **Chapter 5** we present reference values for heart rate variability in young and middle-aged subjects since the lack of reference values limits implementation of heart rate variability analysis in the clinical setting. Furthermore, we defined the influences of gender and age for short-term heart rate variability.

International standards advise standardised test conditions for autonomic function, which consequently limits its implementation during routine preoperative assessment. In **Chapter 6** we evaluated the comparability of autonomic function tests (Ewing tests and heart rate variability) under both non-standardised and standardised test conditions in healthy subjects to evaluate whether autonomic function testing might be simplified for the anaesthesia population.

In **Chapter 7** we aimed to compare autonomic function testing under non-standardised versus standardised test conditions and to investigate the agreement of heart and pulse rate variability in subjects with type II diabetes mellitus and cardiovascular disease.

In **Chapter 8** we investigated the association between preoperative pulse rate variability and intraoperative haemodynamic stability in order to elaborate whether preoperative autonomic function testing might be of predictive value for anaesthesia-related haemodynamic complications.

In **Chapter 9** the mental strain of the surgeon was assessed by means of heart rate variability during conventional and robot-assisted laparoscopic cholecystectomy.

In **Chapter 10** the main results and conclusions of this dissertation are discussed and placed in a broader perspective.

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