# Perioperative hyperglycaemia and its treatment in patients with diabetes mellitus

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# THE PREVALENCE OF CARDIOVASCULAR AUTONOMIC NEUROPATHY AND ITS INFLUENCE ON POST INDUCTION HAEMODYNAMIC PARAMETERS IN PATIENTS WITH AND WITHOUT DIABETES; A PROSPECTIVE COHORT STUDY

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## Abstract

**Objective**: Cardiovascular autonomic neuropathy (CAN) is a known complication of diabetes, but is also diagnosed in patients without diabetes. CAN may be related to perioperative haemodynamic instability. Our objective was to investigate if patients with diabetes would have a higher prevalence of CAN compared to patients without diabetes in the preoperative setting. We further studied the relevance of diagnosing CAN preoperative by studying its relation to changes in post-induction haemodynamic variables.

**Methods:** We prospectively included 82 adult patients, 55 with DM, 27 without DM, scheduled for major abdominal or cardiac surgery. Patients performed four autonomic function tests on the day before surgery. Primary outcomes were the prevalence of CAN and the relation between CAN and severe post-induction hypotension, defined as mean arterial pressure (MAP) < 50 mmHg or ≥ 50% decrease from baseline. Secondary outcomes were the relation between CAN, intraoperative hypotension, MAP < 65 mmHg for more than 13 minutes, and the use of vasopressor therapy.

**Results:** The prevalence of CAN in patients with or without DM was 71% versus 63%, (p=0.437). CAN was not associated with severe post induction hypotension (CAN+ vs. CAN–: 21% vs. 19.2%, p=0.819) nor with intraoperative hypotension (16% vs. 15%, p=0.937). Patients with CAN received more norepinephrine in the postoperative period (0.06 mcg/kg/min (IQR 0.04 – 0.13) vs. 0.04 (IQR 0.02 – 0.05) p=0.033).

**Conclusion**: the majority of patients presenting for major surgery had mild to moderate CAN, regardless of the presence of DM. Assessing CAN before surgery did not identify patients at risk for post induction and intraoperative hypotension in our cohort.

## Introduction

Cardiovascular autonomic neuropathy (CAN) is characterised by an imbalance of the parasympathetic and sympathetic tone and is a well-known complication of diabetes mellitus (DM) (1,2). Although mainly focussed on patients with DM, patients without DM are also known to develop CAN (3,4).

The reported prevalence of CAN is highly variable in patients with and without DM and ranges from 0 to 100%, depending on the duration of DM, glycaemic control and the population studied (5-9). In addition, the relevance of diagnosing CAN before surgery is unclear. Only a handful of studies have assessed the influence of CAN on the perioperative haemodynamic response, some of them showing a relation of CAN with perioperative hypotension, whereas others did not (4,7-11). These studies mainly focussed on patients with DM and used patients without DM as 'healthy control group'. However, patients without DM but with CAN might have the same perioperative risks as patients with DM and CAN.

Autonomic function can be assessed in several ways: we used the Ewing's battery of bedside tests and the baroreflex sensitivity (BRS), as both ways can easily be integrated at the preoperative assessment clinic (12-14). The aim of this study was to use the Ewing test battery and BRS to determine the prevalence of CAN in patients with and without DM undergoing major elective surgery. In addition, we set out to examine the predictive value of this set of autonomic function tests for post-induction hypotension as this could help us to identify high-risk patients at the preoperative assessment clinic.

We hypothesised that patients with DM would have a higher incidence of CAN than patients without DM. Furthermore, we hypothesized that patients with CAN were more likely to experience post-induction hypotension and consequently would require more haemodynamic support with vasopressors.

## Methods

The protocol of this study was approved by the local ethics committee of the Academic Medical Centre in Amsterdam (MEC 2014_242). The study was conducted conform guidelines of good clinical practice and the Declaration of Helsinki (15). Written informed consent was obtained from all patients before participating in this study. Our trial was registered in the Dutch trial register (www.trialregister.nl #4976).

We conducted a single centre prospective cohort study. Participants were included between September 2014 and March 2017. Patient characteristics of adult patients scheduled for elective cardiac or major abdominal surgery were collected at the preoperative assessment clinic. Exclusion criteria were: cardiac rhythm other than sinus rhythm, Parkinson's disease, pure autonomic failure (formerly called idiopathic orthostatic hypotension), multiple system atrophy with autonomic failure (formerly called Shy-Drager syndrome), Addison's disease and hypopituitarism, pheochromocytoma, peripheral autonomic neuropathy (e.g., amyloid neuropathy, idiopathic autonomic neuropathy), known cardiomyopathy, extreme left ventricle hypertrophy (16), ejection fraction < 30% (16) and proven or suspected allergy for any of the medication used during induction of anaesthesia.

*Protocol*

One day before surgery, continuous haemodynamic variables were assessed with the ccNexfin monitor (Edwards Lifesciences Corporation, Irvine, CA, USA) during autonomic and peripheral nervous system testing. The ccNexfin has been validated (17,18) and used before to assess cardiovascular autonomic function (12,13). Ewing's battery of tests originally consisted of five autonomic function tests (19), however we omitted the sustained handgrip test in our series of tests, as this test was found to have limited diagnostic power (20).

*Autonomic function tests (19):*

1. Paced breathing: the patient was asked to take deep breaths with a frequency of 6 per minute for 1 minute. Heart rate (HR) variability between inspiration and expiration was measured. A difference in HR ≥ 15 beats per minute between inspiration and expiration was considered normal, a difference in HR ≤ 10 beats per minute was an indication of parasympathetic neuropathy and considered abnormal. A difference in HR between 11 and 14 beats per minute was considered borderline.

2. Valsalva Manoeuvre: the patient was asked to blow through a mouthpiece with a small leakage of 16 gauge and to maintain a pressure of 40 mmHg for 15 seconds. The leakage ensures an open glottis during the procedure. In normal subjects tachycardia arises during these 15 seconds of strain with a subsequent vasoconstriction. After release of strain a hypertensive response and reflex bradycardia is observed. In patients with both sympathetic and parasympathetic neuropathy, little change is seen in HR and blood pressure. We calculated the ratio between the longest interbeat interval after release and the shortest interbeat interval during strain. A ratio of 1.21 or more was considered normal, a ratio of 1.20 or less was considered abnormal.

3. 30:15 ratio: patients were asked to stand up from a supine position. In healthy subjects, tachycardia after 15 heartbeats with a subsequent bradycardia after 30 heart beats is expected. An abnormal response shows a decrease in 30:15 ratio, which is due to parasympathetic neuropathy. A ratio of 1.04 or more was considered normal, a ratio of 1.01 to 1.03 was considered borderline and a ratio of 1.00 or less was considered abnormal. Because these time constants are not equal for every subject, the shortest interbeat interval around the $15^{th}$ beat and the longest interbeat interval around the $30^{th}$ beat were used for this calculation (21).

4. Orthostatic response: the patients were asked to stand up from a supine position and to remain standing for three minutes. If blood pressure remains low after three minutes of standing, this is an indication for sympathetic neuropathy. A fall in systolic blood pressure (SBP) of 10 mmHg or less after three minutes was considered normal. A fall in SBP of 11-29 mmHg after three minutes was considered borderline and a fall in SBP of 30 mmHg or more after three minutes was considered abnormal.

*Baroreflex sensitivity (BRS)*

1. To calculate BRS, thirty seconds of data during paced breathing at 6 $min^{-1}$ were extracted and equidistantly resampled at 0.1 Hz. SBP (in mmHg) was plotted against the interbeat interval in milliseconds (inverse of HR). There is a small latency between variations in systolic blood pressure and HR. We shifted the HR tracing 1-3 seconds to obtain the highest correlation (Pearson R) between SBP and HR. The slope of the linear regression line between SBP and HR equals BRS expressed as ms $mmHg^{-1}$. Higher values indicate better autonomic function (22,23).

Anaesthesia was induced according to a standardised regimen with propofol (range 0.8 to 2.5 mg $kg^{-1}$), sufentanil (range 0.2 to 0.5 mcg $kg^{-1}$) and rocuronium (range 0.5 to 1.0 mg $kg^{-1}$). Furthermore, when an epidural catheter was placed, no epidural medication was administered during the first 10 minutes after induction.

Intra operative haemodynamic variables from T0 (start induction) to T10 (10 minutes after induction) and from T30 to T60 were collected from the electronic perioperative charts, containing haemodynamic measurements at least every 5 minutes. Additionally, the use of vasopressor or inotropic support during surgery and in the postoperative period was collected via electronic chart review.

*Outcome measures*

As primary outcome measure we calculated the prevalence of CAN in patients with or without DM and used a modified version of the classification of CAN originally proposed

by Ewing (19): *normal stage*: all tests normal, or one borderline. *Early stage*: abnormal response to one of the tests with or without one borderline test or two tests borderline (either HR or blood pressure). *Definite stage*: abnormal response to two tests with or without one borderline test (HR or blood pressure). *Severe stage*: abnormal response to two of the three HR tests plus abnormal response to the blood pressure test. Additionally, the BRS was calculated to express heart rate variability in response to blood pressure on a continuous scale.

Our other main outcome measure was the difference in the incidence of severe post-induction hypotension, comparing patients with and without CAN. Severe post-induction hypotension was defined as a mean arterial pressure (MAP) of < 50 mmHg or a ≥ 50% decrease in MAP from baseline. This is based on the recent publication by Salmasi et al (24), showing that these values were associated with a higher odds for developing acute kidney injury (AKI) or myocardial injury after non-cardiac surgery (MINS) when they occurred for > 1 minute (24). This is a slight modification of our original definition (MAP<55 mmHg, www.trialregister.nl #4976), because the paper of Salmasi was published after trial registration. Baseline blood pressure was defined as the blood pressure measured at the preoperative assessment clinic. In case of a missing value, we used the blood pressure measured by a nurse on the ward one day prior to surgery (25). We selected T0 to T10 (10 minutes), as timeframe for the induction of anaesthesia.

As secondary outcome measures during induction of anaesthesia we evaluated mild post-induction hypotension: MAP < 65 mmHg. A MAP below 65 mmHg for more than 13 minutes was also associated with greater odds in developing AKI or MINS (24). Change in SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP) and HR when the trachea was intubated and the need for phenylephrine and ephedrine during induction of anaesthesia were assessed.

In addition we evaluated the average SBP, DBP, MAP and HR during the 'stable phase of anaesthesia'. Furthermore, the mean absolute blood pressure change was calculated as a measure of blood pressure swings intraoperatively. Intraoperative hypotension was defined as a MAP < 65 for more than 13 minutes (24). Low systolic blood pressure (LSBP) was defined as a systolic blood pressure <90 mmHg at any time during the stable phase of anaesthesia. To avoid bias from intraoperative events (for example cardiopulmonary bypass or significant surgical blood loss) we chose T30 to T60 as timeframe for the 'stable phase of anaesthesia', to assess intraoperative haemodynamic variables. If initiation of cardiopulmonary bypass was within these 30 minutes, data collection was ceased at that point. The total intraoperative dose of norepinephrine (mcg kg-1 min-1), total postoperative dose of norepinephrine (mcg $kg^{-1}$ $min^{-1}$) and duration of cardiovascular

support (in hours) was evaluated. Finally, risk factors for severe and mild post-induction hypotension were explored in multivariate regression.

*Sample size*

A previous study by Knuttgen et al. showed that 72.2% of patients with DM and evidence of CAN experienced hypotension after induction, compared to 25% of patients without DM (11). Assuming a power of 80% and a significance level of 0.05 we needed a minimum sample size of 14 patients per group to detect such a difference. Assuming that we would diagnose a form of CAN in 50% of patients with DM (10) with a dropout of 5%, our minimal sample size was 45 patients (30 with DM and 15 without DM).

In order to be able to also perform a subgroup analysis between cardiac and abdominal surgery, we aimed for the inclusion of 90 patients: 45 patients (30 with DM, 15 without DM) undergoing cardiac surgery and 45 patients (30 with DM, 15 without DM) undergoing abdominal surgery.

*Data handling and statistics*

Data were extracted, encrypted and stored for offline analysis. Data were manually checked for quality and tests with artefacts (non-sinus rhythm during the autonomic function tests, evidence of poor calibration of the ccNexfin during the measurements) were rejected. Hereafter, data were analysed in Matlab (2007b, MathWorks, Natick, MA, USA). If data from one test was not analysable, we considered this test to be normal, knowing that this would lead to a possible underestimation of the prevalence of CAN. In case the anaesthesiologist did not comply with the standardised induction protocol, patients were excluded from the analyses.

Patient characteristics were listed for all patients and separately for patients with and without DM. Differences between the two groups were assessed with a Student's t-test or Mann Whitney-U test, depending on the distribution of the data. Normality was evaluated with the Shapiro-Wilk test. The BRS calculated from the paced breathing was plotted against the stages of CAN, to evaluate their level of agreement. Univariate analysis was done with a Chi-square test or non-parametric test, to evaluate the association between CAN and the haemodynamic variables. The mean absolute blood pressure change was defined as the absolute change between two adjacent blood pressure measurements divided over the time in which they were measured. In other words: it is the sum of all absolute blood pressure differences divided by 30 minutes (mmHg $min^{-1}$) (26). In 16/82 cases, blood pressure was measured every three minutes instead of every minute, missing data was imputed with a linear coefficient. Receiver operating characteristic (ROC) curves were plotted to evaluate the association between BRS and

severe or mild post-induction hypotension. Reported p-values are 2-sided. A p-value < 0.05 was assumed to indicate statistical significant differences.

## Results

We assessed 295 patients for potential inclusion in this study. In total, 101 patients consented and underwent autonomic function testing. Nineteen patients were subsequently excluded due artefacts in the autonomic function tests or non-compliance with the induction protocol (figure 1). Eighty-two patients were included in the final analyses.

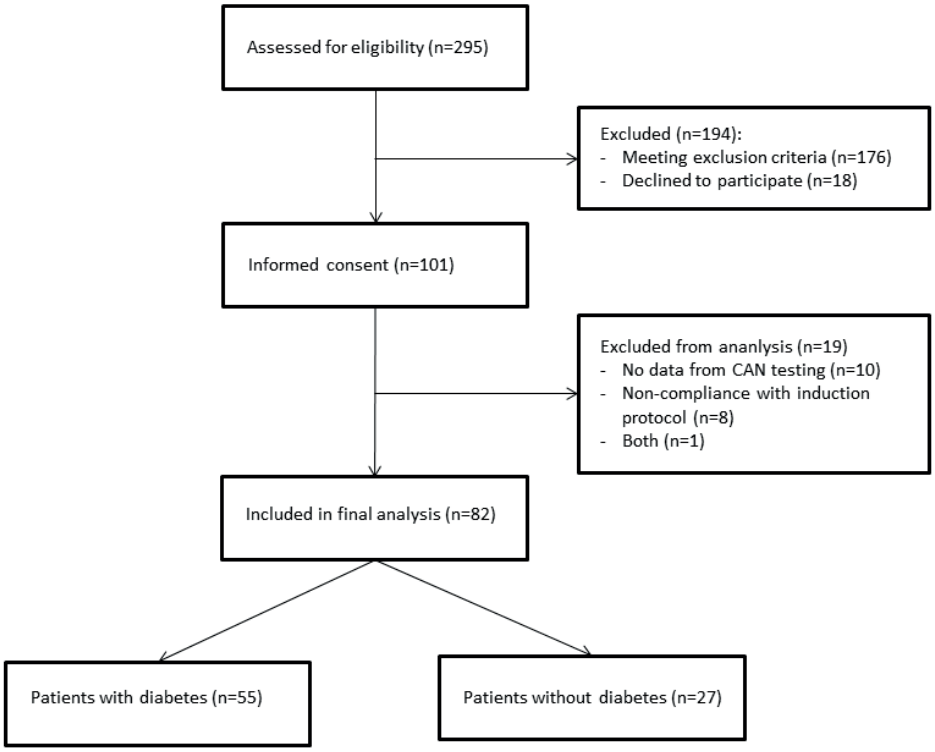


**Figure 1.** Flow chart of study

Patient characteristics are displayed in table 1. Patients with DM were more often diagnosed with arterial hypertension and consequently used more beta-blockers, angiotensin converting enzyme inhibitors and angiotensin 2 receptor blockers.

**Table 1:** Patient characteristics

| | All patients (n=82) | Diabetes + (n=55) | Diabetes – (n=27) | p-value |
|---|---|---|---|---|
| Male | 58 (70.7) | 36 (65.5) | 22 (81.5) | .134 |
| Age (years) | 63 (11) | 64 (10) | 62 (12) | .499 |
| *ASA classification status* | | | | .064 |
| ASA I | 2 (2.4) | - | 2 (7.4) | |
| ASA II | 34 (41.5) | 21 (38.2) | 13 (48.1) | |
| ASA III | 46 (56.1) | 34 (61.8) | 12 (44.4) | |
| *History of*: | | | | |
| Hypertension | 43 (52.4) | 35 (63.6) | 8 (29.6) | **.004** |
| Myocardial infarction | 20 (24.4) | 16 (29.1) | 4 (14.8) | **.**157 |
| Aorta valve stenosis | 18 (22.0) | 10 (18.2) | 8 (29.6) | .239 |
| Malignancy | 27 (32.9) | 17 (30.9) | 10 (37.0) | .579 |
| *Anti-hypertensive medication* | | | | |
| ACE/AT2 inhibitors | 35 (42.7) | 28 (50.9) | 7 (25.9) | **.032** |
| Beta blockers | 35 (42.7) | 29 (52.7) | 6 (22.2) | **.009** |
| Calcium channel blockers | 15 (18.3) | 13 (23.6) | 2 (7.4) | .126 |
| Diuretics | 16 (19.5) | 14 (25.5) | 2 (7.4) | .075 |
| *Baseline haemodynamic variables* | | | | |
| Systolic blood pressure (mmHg) | 141 (20.6) | 141 (19.7) | 142 (22.8) | .821 |
| Diastolic blood pressure (mmHg) | 80 (10.2) | 80 (10.5) | 82 (9.7) | .392 |
| Mean arterial pressure (mmHg) | 101 (12.0) | 100 (12.2) | 102 (11.9) | .540 |
| Heart rate (beats $min^{-1}$) | 74 (11.9) | 76 (11.9) | 72 (11.5) | .181 |
| *Diabetes related*: | | | | |
| Diabetes | 55 (67.1) | - | - | - |
| Duration of diabetes (median [IQR],years) | 7.5 (4 – 17) | 7.5 (4 – 17) | - | - |
| HbA1C (median [IQR],mmol $mol^{-1}$) | 53 (45 – 67) | 53 (45 – 67) | - | - |
| Treated with insulin | 28 (34.1) | 28 (50.9) | - | - |
| Peripheral neuropathy | 23 (28.0) | 22 (40.0) | 1 (3.7) | **.003** |
| Retinopathy | 2 (2.4) | 2 (3.6) | - | - |
| Nephropathy | 6 (7.3) | 6 (10.9) | - | - |
| Fasting glucose (median [IQR], mmol $l^{-1}$) | | 7.7 (6.7 – 9.5) | 5.8 (5.4 – 8.2) | <.001 |
| *Type of surgery* | | | | **.**941 |
| Cardiac surgery | 39 (47.6) | 26 (47.3) | 13 (48.1) | |
| Abdominal surgery | 43 (52.4) | 29 (52.7) | 14 (51.9) | |
| Duration of surgery (min) | 222 (78) | 215 (73) | 236 (87) | .258 |

Values are: number (%) or mean (SD) unless otherwise specified. (ACE/AT2) angiotensin converting enzyme / angiotensin 2 receptor; (HbA1c) glycosylated haemoglobin; (IQR) interquartile range

There was no difference in the prevalence of CAN between patients with or without DM (p=0.437). Out of the patients with DM, 39 (71%) had either early or definite CAN. Out of the patients without DM, 17 (63%) had either early or definite CAN (figure 2). We did not identify patients with severe stage of CAN. The BRS was in agreement with the different

stages of CAN (figure 3a), there was no difference in BRS for patients with or without DM (figure 3b).

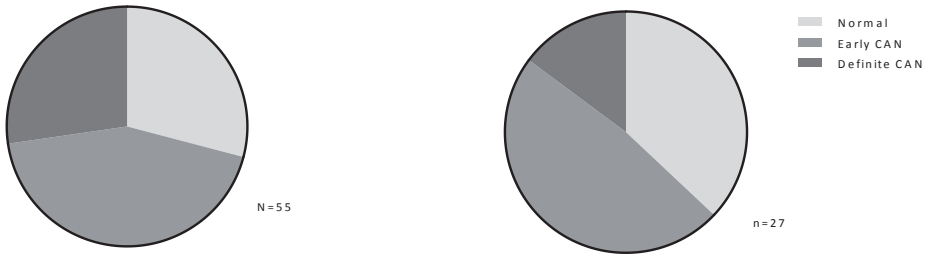


**Figure 2.** Prevalence of CAN; left panel: patients with DM (n=55), right panel: patients without DM (n=27)

Univariate analyses showed that patients with CAN did not display an increased incidence of severe or mild post-induction hypotension compared to patients without CAN (21% vs. 19%, p=0.819 and 46% vs. 31%, p=0.180 respectively), nor were there any other differences in haemodynamic post-induction variables between patients with and without CAN (table 2). The ROC curve showed that the BRS was not associated with severe or mild post-induction hypotension (AUC 0.53, 95%CI 0.34 – 0.72 and AUC 0.42, 95%CI 0.28 – 0.56). Subanalysis comparing patients with versus without DM, definite CAN versus no CAN and subgroup analysis for cardiac and abdominal surgery did not yield any different results (appendix 1).

**Table 2:** Univariate analysis association CAN and post-induction haemodynamic variables

| | CAN + (n=56) | CAN– (n=26) | p-value |
|---|---|---|---|
| Diabetes | 39 (69.6) | 16 (61.5) | .467 |
| Severe post-induction hypotension | 12 (21.4) | 5 (19.2) | .819 |
| Mild post-induction hypotension | 26 (46.4) | 8 (30.8) | .180 |
| Delta SBP post-intubation (mmHg) | 16 (4 – 52) | 20 (5 – 44) | .998 |
| Delta MAP post-intubation (mmHg) | 8 (1 – 34) | 18 ( 3 – 31) | .634 |
| Delta DBP post-intubation (mmHg) | 10 (1 – 27) | 15 (2 – 30) | .694 |
| Delta HR post-intubation (beats $min^{-1}$) | 11 (3 – 20) | 14 (5 – 19) | .651 |
| Patients receiving phenylephrine or ephedrine post-induction | 17 (30.4) | 9 (34.6) | .700 |
| Dose phenylephrine post-induction (microgram) | 100 (100 – 200) | 100 (100 – 175) | .603 |
| Dose ephedrine post-induction (milligram) | 7.5 (5 – 10) | 10 (5 – 10) | 1.000 |

Values are number (%) or median (IQR). (SBP) systolic blood pressure, (MAP) mean arterial pressure, (DBP), diastolic blood pressure, (HR) heart rate

Intraoperative hypotension occurred in 9 (16 %) patients with CAN and 4 (15%) patients without CAN (p=0.937). Also, the incidence of low systolic blood pressure did not differ

between patients with or without CAN (61% vs. 62%). Furthermore, the intraoperative haemodynamic variables did not differ between patients with or without CAN (table 3). Patients with CAN did receive more norepinephrine postoperatively (0.06 mcg $kg^{-1}$ $min^{-1}$ (0.04 – 0.13) vs. 0.04 (0.02 – 0.05) p=0.033).

**Table 3:** Univariate analyses, association of CAN and intraoperative haemodynamic variables

| | CAN + (n=56) | CAN– (n=26) | p-value |
|---|---|---|---|
| Average SBP intraoperative (mmHg) | 112 (14.2) | 110 (12.3) | .550 |
| Average MAP intraoperative (mmHg) | 77 (8.9) | 79 (9.2) | .351 |
| Average DBP intraoperative (mmHg) | 60 (8.7) | 64 (9.4) | .066 |
| Average HR intraoperative (beats $min^{-1}$) | 61 (9.1) | 65 (10.8) | .060 |
| Mean absolute SBP change (mmHg) | 5.5 (2.1) | 5.1 (2.4) | .500 |
| Mean absolute DBP change (mmHg) | 3.0 (1.2) | 3.7 (1.9) | .058 |
| Mean absolute MAP change (mmHg) | 4.1 (1.2) | 4.4 (1.7) | .404 |
| Mean absolute HR change (beats $min^{-1}$) | 2.3 (1.6) | 2.4 (1.4) | .681 |
| Patients receiving norepinephrine perioperative | 52 (92.9) | 21 (80.8) | .103 |
| Norepinephrine perioperative (median [IQR] mcg $kg^{-1}$ $min^{-1}$) | 0.04 (0.02 – 0.06) | 0.02 (0.00 – 0.05) | .073 |
| Patients receiving norepinephrine postoperative | 20 (35.7) | 10 (38.5) | .810 |
| Total dose norepinephrine postoperative (median [IQR] mcg $kg^{-1}$ $min^{-1}$) | 0.06 (0.04 – 0.13) | 0.04 (0.02 – 0.05) | .033 |
| Duration of norepinephrine postoperative (hrs) | 3.0 (1.8 – 8.9) | 3.0 (2.0 – 8.5) | .951 |

Values are mean (SD) or number (%) unless otherwise specified. (SBP) systolic blood pressure, (MAP) mean arterial pressure, (DBP), diastolic blood pressure, (HR) heart rate, (hrs) hours

## Discussion

Contrary to our expectation, the incidence of CAN in patients with DM was comparable to patients without DM. Diagnosing CAN before surgery did not identify patients at risk for perioperative hypotension.

We found a fairly high rate (63%) of CAN in patients without DM. The Ewing's battery of tests was designed to diagnose CAN in patients with DM (27). Previous studies in surgical patients and in patients after a myocardial infarction, including patients with and without DM, have reported slightly lower prevalence's of 35-50%, using comparable cut-off values (9,11,23,28). Apart from diabetes, also advancing age, hypertension, heart failure and previous myocardial infarction are known risk factors for developing CAN (3,29,30). A significant part of our study population had at least one of these risk factors. This might explain why a significant part of our patients without DM also complied with

the criteria for early CAN. This emphasizes that research on the relation between CAN and haemodynamic variables should not be limited to patients with DM.

Our data suggest that the BRS might be a valid replacement for Ewing's battery of tests to assess CAN. This has been suggested before in patients with DM (31,32), but has never been shown for patients without DM. The Ewing's battery of tests lasts about 20 to 30 minutes to be completed and required a cooperative patient. To calculate the BRS, one only has to do the paced breathing test, which takes two minutes at most. The mean BRS in patients with mild stage of CAN was 5.6 ms $mmHg^{-1}$ (figure 3). Previously, a cut-off value of < 6 ms $mmHg^{-1}$ was classified as moderate depressed BRS and associated with cardiac mortality after a myocardial infarction in a large prospective cohort study (28). Furthermore, a BRS < 6 ms $mmHg^{-1}$ was found to correlate well with postoperative infections and cardiovascular morbidity in a post-hoc analysis of a randomised controlled trial (23).

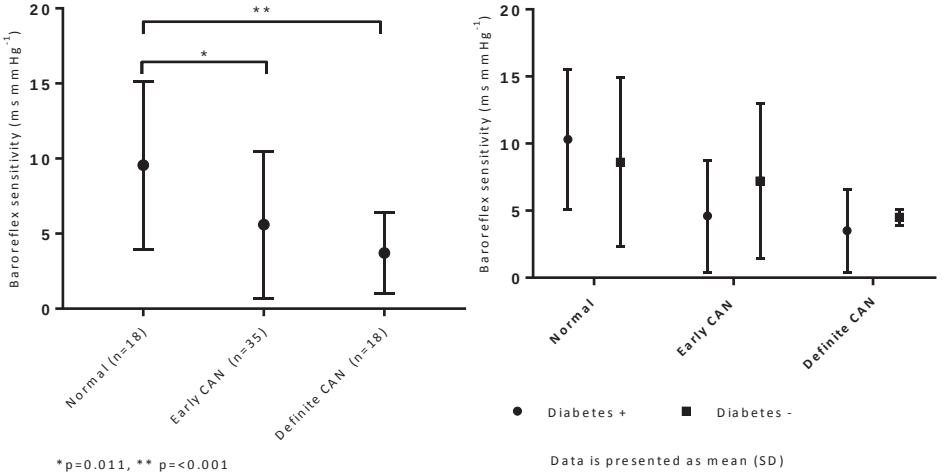


**Figure 3.** Level of agreement between stages of CAN and the baroreflex sensitivity
Left panel: including all patients
Right panel: separate for patients with and without DM
Values are mean BRS (SD). *p=0.011, **p<0.001

As opposed to most studies from the early 90's on CAN and perioperative hypotension (4,9-11), we could not establish a relation between CAN and post-induction or intraoperative hypotension. This might be due to the difference in populations studied, differences in induction protocol or differences in intraoperative blood pressure targets: The studies which found a relation between hypotension and CAN were performed in patients undergoing minor (ophthalmologic or ambulatory) surgery (4,9-11). Indeed, our results are in agreement with one study who also studied patients subjected to

major (cardiac) surgery (8). Especially patients undergoing cardiac surgery have numerous reasons other than CAN to become hypotensive during surgery; they often use more than one antihypertensive agent and might have a reduced myocardial function. Furthermore, as the optimal induction protocol for patients with CAN is not known, every study had their own unique induction protocol. Finally, the field of anaesthetic practice has evolved between the early 90's and 2017. Anaesthetic research and care today is more focussed on preventing postoperative morbidity and mortality, and intraoperative hypotension has been related to both (24,33-35). Although the definition of intraoperative hypotension might not have changed substantially over the years, the anaesthesiologist might be more focussed on preventing hypotension compared to 30 years ago (24,36,37). This may also be reflected by the slightly lower incidence of intraoperative hypotension (systole < 90 mmHg) in our cohort (61%) compared to 75% in the study by Knuttgen et al (11).

There are many definitions for baseline blood pressure or intraoperative hypotension (24,25,36). We assessed for three different definitions if post-induction or intraoperative hypotension was associated with CAN, as these definitions were related to postoperative morbidity: severe (MAP<50 mmHg or ≥ 50% decrease from baseline) and mild (MAP < 65mmHg) post-induction hypotension, intraoperative hypotension (MAP < 65 for > 13 minutes) (24). We also assessed whether intraoperative low systolic blood pressure (systole < 90mmHg) was associated with CAN as this was the definition used by Knuttgen et al (11). Although the incidences of post-induction and intraoperative hypotension varied per definition used (15% to 62%), we could not detect any difference between patients with and without CAN for any of these definitions.

Postoperatively, patients with CAN received significantly more norepinephrine compared to patients without CAN. Although this finding could be due to chance and multiple statistical testing, we hypothesise that anaesthesia related impairment of the autonomic system obscures any contribution of DM related autonomic dysfunction during the procedure, but this effect may be reversed when the patient emerges from anaesthesia. Toner et al showed that a preoperative BRS < 6 ms $mmHg^{-1}$ was significantly associated with a postoperative BRS < 6 ms $mmHg^{-1}$ (23). Unfortunately, an intraoperative BRS was not calculated. However, these results suggest that baseline BRS might be a good marker for postoperative morbidity. It would therefore be of interest to prospectively measure the BRS preoperatively, intraoperatively and postoperatively combined with the assessment of postoperative complications. Such a study might answer the question whether the BRS can identify patients in need for a more extensive postoperative monitoring. Unfortunately, our study lacks power to be able to comment on postoperative outcomes.

A limitation of our study is the lack of standardization of a target MAP and protocollised use of vasopressors or inotropic agents, which could have biased our results. However, the induction of anaesthesia was standardised. Furthermore, we had to exclude 11 patients based on insufficient quality of the beat-to-beat data during the autonomic function tests and eight patients based on non-compliance with the induction protocol. Nonetheless, the patient characteristics of the excluded patients were comparable with the study population and we have no reason to believe that these 19 patients would have altered our results. Lastly, our sample size calculation was based on a study reporting a large difference in the incidence of intraoperative hypotension (75% vs 25%) We did not detect this huge difference in our study (21% vs 19%). Knuttgen et al. defined hypotension as a systolic blood pressure below 90 mmHg. We chose to define hypotension according to the most recent literature as this was related to postoperative morbidity (24). However, when we used the definition of a systolic blood pressure < 90 mmHg in our cohort, the incidence of hypotension was 61% vs. 62%, p=0.943 (CAN+ vs. CAN–). Furthermore, we could not detect a difference between patients with and without CAN for all other secondary outcome measures. In addition, the study was sufficiently powered, as we needed 14 patients per group (healthy, CAN with DM and CAN without DM) for our main analyses and in the end included 82 patients, with a higher incidence of CAN than expected.

To summarise, 65 to 70% of patients presenting for major surgery had mild to moderate CAN, regardless of their diagnosis of DM. Diagnosing CAN did not identify patients at risk for post-induction or intraoperative hypotension and is not recommended. However, whether CAN is predictive for the risk of postoperative haemodynamic instability or complications remains an open question.

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## Supplementary tables

**Table 1.** Post-induction hemodynamic parameters comparing CAN+ vs. CAN-, apart for patients with and without DM

| | Diabetes + (n=55) | | | Diabetes – (n=27) | | |
|---|---|---|---|---|---|---|
| | CAN + (n=39) | CAN– (n=16) | p-value | CAN + (n=17) | CAN – (n=10) | p-value |
| Severe post-induction hypotension | 7 (17.9) | 3 (18.8) | .944 | 2 (11.8) | 2 (20.0) | .561 |
| Mild post-induction hypotension | 21 (53.8) | 5 (31.3) | .127 | 5 (29.4) | 3 (30.0) | .974 |
| Delta MAP post-intubation | 8 (0 – 34) | 18 (4 – 31) | .642 | 13 (1 – 30) | 19 (-1– 42) | .934 |
| Delta HR post-intubation | 9 (2 – 20) | 10 (3 – 20) | .805 | 12 (3 – 19) | 14 (7 – 21) | .223 |
| Patients receiving norepinephrine perioperative | 37 (94.9) | 15 (93.8) | .868 | 15 (88.2) | 6 (60.0) | .088 |
| Norepinephrine perioperative (mcg $kg^{-1}$ $min^{-1}$) | 0.04 (0.02 –0.06) | 0.03 (0.02 – 0.06) | .505 | 0.03 (0.02 – 0.07) | 0.01 (0.003 – 0.03) | .056 |
| Patient receiving norepinephrine postoperative | 13 (33.3) | 6 (37.5) | .786 | 7 (41.2) | 4 (40.0) | .952 |
| Total norepinephrine postoperative (mcg $kg^{-1}$ $min^{-1}$) | 0.08 (0.05 – 0.16) | 0.05 (0.03 – 0.07) | .161 | 0.05 (0.04 – 0.07) | 0.03 (0.02 – 0.04) | .072 |
| Hours norepinephrine postoperative | 3.0 (1.5 – 6.9) | 8.0 (2.0 – 14.0) | .233 | 4.0 (2.0 – 24.0) | 2.5 (1.3 – 3) | .152 |

Values are n (%) or median ($25^{th}$ – $75^{th}$ percentile). MAP: mean arterial pressure, HR: heart rate, CAN: cardiovascular autonomic neuropathy

**Table 2.** Post-induction hemodynamic parameters comparing DM+ versus DM-, apart for patients with CAN+ and CAN-

| | CAN + (n=56) | | | CAN – (n=26) | | |
|---|---|---|---|---|---|---|
| | DM + (n=39) | DM– (n=17) | p-value | DM + (n=16) | DM – (n=10) | p-value |
| Severe post-induction hypotension | 7 (17.9) | 2 (11.8) | .562 | 3 (18.8) | 2 (20.0) | .937 |
| Mild post-induction hypotension | 21 (53.8) | 5 (29.4) | .092 | 5 (31.3) | 3 (30.0) | .946 |
| Delta MAP post-intubation | 8 (0 – 34) | 13 (1 – 30) | .785 | 18 (4 – 31) | 19 (-1– 42) | .987 |
| Delta HR post-intubation | 9 (2 – 20) | 12 (3 – 19) | .964 | 10 (3 – 20) | 14 (7 – 21) | .523 |
| Patients receiving norepinephrine perioperative | 37 (94.9) | 15 (88.2) | .375 | 15 (93.8) | 6 (60.0) | .034 |
| Norepinephrine perioperative (mcg $kg^{-1}$ $min^{-1}$) | 0.04 (0.02 – 0.06) | 0.03 (0.02 – 0.07) | .417 | 0.03 (0.02 – 0.06) | 0.01 (0.003 – 0.02) | .058 |
| Patient receiving norepinephrine postoperative | 13 (33.3) | 7 (41.2) | .573 | 6 (37.5) | 4 (40.0) | .899 |
| Total norepinephrine postoperative (mcg $kg^{-1}$ $min^{-1}$) | 0.08 (0.05 – 0.16) | 0.05 (0.04 – 0.07) | .251 | 0.05 (0.03 – 0.07) | 0.03 (0.0.2 – 0.04) | .136 |
| Hours norepinephrine postoperative | 3.0 (1.5 – 6.9) | 4.0 (2 – 24) | .211 | 8.0 (2 – 14) | 2.5 (1.3 -3.0) | .164 |

Values are n (%) or median ($25^{th}$ – $75^{th}$ percentile). MAP: mean arterial pressure, HR: heart rate, CAN: cardiovascular autonomic neuropathy.

**Table 3.** Subgroup analysis for patients presenting for cardiothoracic surgery

| | CAN + (n=26) | CAN – (n=13) | p-value |
|---|---|---|---|
| Severe post-induction hypotension | 4 (15.4) | 2 (15.4) | 1.00 |
| Mild post-induction hypotension | 13 (50.0) | 5 (38.5) | .496 |
| Delta MAP post-intubation | 8 (3 – 36) | 4 (0– 18) | .412 |
| Delta HR post-intubation | 6 (2 – 17) | 5 (3 – 11) | .703 |
| Patients receiving norepinephrine perioperative | 26 (100) | 11 (84.6) | 0.04 |
| Total norepinephrine perioperative (mcg $kg^{-1}$ $min^{-1}$) | 0.04 (0.01 – 0.08) | 0.02 (0.01 – 0.06) | .180 |
| Patients receiving norepinephrine postoperative | 17 (65.4) | 8 (61.5) | .813 |
| Total norepinephrine postoperative (mcg $kg^{-1}$ $min^{-1}$) | 0.06 (0.04 – 0.11) | 0.04 (0.03 – 0.06) | .130 |
| Hours norepinephrine postoperative | 3.0 (1.8 – 6.9) | 4.0 (1.5 – 11.3) | .807 |

Values are n (%) or median ($25^{th}$ – $75^{th}$ percentile). MAP: mean arterial pressure, HR: heart rate, CAN: cardiovascular autonomic neuropathy

**Table 4.** Subgroup analysis for patients presenting for abdominal surgery

| | CAN + (n=30) | CAN – (n=13) | p-value |
|---|---|---|---|
| Severe post-induction hypotension | 5 (16.7) | 3 (23.1) | .620 |
| Mild post-induction hypotension | 13 (43.3) | 3 (23.1) | .207 |
| Delta MAP post-intubation | 15 (-2 – 34) | 27 (19 – 37) | .221 |
| Delta HR post-intubation | 12 (4 – 22) | 18 (15 – 25) | .091 |
| Patients receiving norepinephrine perioperative | 26 (86.7) | 10 (76.9) | .427 |
| Total norepinephrine perioperative (mcg $kg^{-1}$ $min^{-1}$) | 0.04 (0.02 – 0.05) | 0.02 (0.004 – 0.05) | .245 |
| Patients receiving norepinephrine postoperative | 3 (10.0) | 2 (15.4) | .613 |
| Total norepinephrine postoperative (mcg $kg^{-1}$ $min^{-1}$) | 0.09 (0.07 – 0.35) | 0.03 (0.01 – 0.04) | .083 |
| Hours norepinephrin postoperative | 11 (9.0) | n/a | n/a |

Values are n (%) or median ($25^{th}$ – $75^{th}$ percentile). MAP: mean arterial pressure, HR: heart rate, CAN: cardiovascular autonomic neuropathy

**Table 5.** Post-induction hemodynamic parameters comparing definite CAN versus no CAN.

| | CAN definite (n=19) | CAN– (n=26) | p-value |
|---|---|---|---|
| Diabetes | 15 (79) | 16 (62) | .213 |
| Severe post-induction hypotension | 4 (21.1) | 5 (19.2) | .880 |
| Mild post-induction hypotension | 10 (52.6) | 8 (30.8) | .139 |
| Delta SBP post-intubation (mmHg) | 9 (1 – 50) | 20 (5 – 44) | .414 |
| Delta MAP post-intubation (mmHg) | 8 (3 – 34) | 18 ( 3 – 31) | .679 |
| Delta DBP post-intubation (mmHg) | 10 (2 – 27) | 15 (2 – 30) | .908 |
| Delta HR post-intubation (beats $min^{-1}$) | 13 (0 – 20) | 14 (5 – 19) | .827 |
| Patients receiving phenylephrine or ephedrine post-induction | 8 (42.1) | 9 (34.6) | .609 |
| Dose phenylephrine post-induction (microgram) | 100 (100 – 200) | 100 (100 – 175) | .603 |
| Dose ephedrine post-induction (milligram) | 7.5 (5 – 10) | 10 (5 – 10) | 1.000 |

Values are n (%) or median ($25^{th}$ – $75^{th}$ percentile). SBP: systolic blood pressure, MAP: mean arterial pressure, DBP: diastolic blood pressure, HR: heart rate, CAN: cardiovascular autonomic neuropathy

**Table 6.** Intraoperative hemodynamic parameters comparing definite CAN versus no CAN

| | CAN definite (n=19) | CAN– (n=26) | p-value |
|---|---|---|---|
| Intraoperative hypotension (mean <65mmHg) | 6 (32) | 4 (15) | .197 |
| Average SBP intraoperative (mmHg) | 110 (1.9) | 110 (12.3) | .941 |
| Average MAP intraoperative (mmHg) | 74 (8.4) | 79 (9.2) | .059 |
| Average DBP intraoperative (mmHg) | 55 (8.0) | 64 (9.4) | .003 |
| Average HR intraoperative (beats $min^{-1}$) | 61 (10.9) | 65 (10.8) | .222 |
| Mean absolute SBP change (mmHg) | 6.5 (2.3) | 5.1 (2.4) | .059 |
| Mean absolute DBP change (mmHg) | 3.4 (1.2) | 3.7 (1.9) | .539 |
| Mean absolute MAP change (mmHg) | 4.3 (1.4) | 4.4 (1.7) | .867 |
| Mean absolute HR change (beats $min^{-1}$) | 2.3 (2.0) | 2.4 (1.4) | .890 |
| Patients receiving norepinephrine perioperative | 19 (100) | 21 (100) | 1.0 |
| Norepinephrine perioperative (median [IQR] mcg $kg^{-1}$ $min^{-1}$) | 0.06 (0.04 – 0.08) | 0.02 (0.00 – 0.05) | .001 |
| Patients receiving norepinephrine postoperative | 9 (47.4) | 10 (38.5) | .810 |
| Total dose norepinephrine postoperative (median [IQR] mcg $kg^{-1}$ $min^{-1}$) | 0.08 (0.05 – 0.11) | 0.04 (0.02 – 0.04) | .028 |
| Duration of norepinephrine postoperative (hrs) | 7.0 (1.1 – 16.5) | 3.0 (2.0 – 8.5) | .552 |

Values are n (%) or mean (SD) unless otherwise specified. SBP: systolic blood pressure, MAP: mean arterial pressure, DBP: diastolic blood pressure, HR: heart rate, CAN: cardiovascular autonomic neuropathy