Indian Journal of Clinical Anaesthesia 2023;10(4):334–339

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical Anaesthesia

Journal homepage: www.ijca.in

Original Research Article

Pre-operative screening of diabetic patients for heart rate variability and their hemodynamic responses during induction of general anaesthesia

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ARTICLE INFO

Article history:
Received 08-09-2023
Accepted 09-10-2023
Available online 28-11-2023

Keywords:
Anaesthesia
Cardiac autonomic neuropathy
Diabetes mellitus
Heart rate variability
Hypotension

ABSTRACT

Background: Cardiovascular autonomic neuropathy (CAN) is one of the least frequently diagnosed and the most clinically significant complications of Diabetes mellitus (DM). Impaired heart rate variability (HRV) is the earliest indicator of CAN. Peri-operative hemodynamic instability is a major concern during general anaesthesia (GA) in patients with autonomic dysfunction. Purpose of this study was to assess and compare the autonomic function using HRV in diabetic and non-diabetic patients pre-operatively and to study the haemodynamic responses of these patients during induction.

Objectives: The primary objective was to assess and compare the autonomic function using HRV in diabetic and non-diabetic patients preoperatively. Secondary objective was to study hemodynamic responses of these patients during induction of GA.

Materials and Methods: We included 68 patients (34 diabetics- group D and 34 non-diabetics- group N) aged between 30 to 65 years, with American society of anaesthesiologists (ASA) physical status 1 and 2 undergoing elective surgeries under GA. All the eligible patients underwent HRV evaluation for 10 minutes on the previous day of surgery and the time & frequency domain variables were evaluated. The hemodynamic parameters were recorded at pre-induction, post-induction, post-intubation and for every 3 minutes thereafter for 15 minutes and analysed.

Results: The diabetics had a significantly lower total power (TP) with p-value 0.003. The post- induction mean arterial pressures (MAP) were comparatively lower in diabetics and the difference was significant at 12 minutes post intubation (p= 0.04). The lower trends in heart rate (HR) were comparatively more in diabetics rather than non-diabetics (p= 0.06) and the ephedrine usage was also higher in diabetics (p= 0.07).

Conclusion: The measurement of HRV is a simple tool to evaluate the peri-operative risks in patients with suspected cardiovascular autonomic neuropathy.

1. Introduction

Type 2 Diabetes mellitus (DM) is the most common type of diabetes in the world, characterized by chronic hyperglycaemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action or both.[1] Diabetic neuropathy occurs in more than 50% of individuals with long standing DM & may manifest as autonomic neuropathy.

Cardiac autonomic neuropathy (CAN) results from damage to the fibres of the autonomic nervous system (ANS) with associated abnormalities of HR control and

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https://doi.org/10.18231/j.ijca.2023.071
2394-4781/© 2023 Author(s), Published by Innovative Publication.

vascular dynamics.[2] Impaired regulation of heart rate and blood pressure causes imbalances in myocardial oxygen demand and supply, which increases the risk of ischemic heart disease, lethal arrythmias and sudden cardiac death.[3] CAN might be subclinical for several years until the patient develops postural hypotension, resting tachycardia, exercise intolerance, hypoglycaemia, unawareness, post prandial hypotension, cardiac dysfunction and diabetic cardiomyopathy.[4] Therefore, the relationship between CAN & perioperative hemodynamic regulation is important.

Heart rate variability (HRV) mainly occurs due to variation in cardiac activities during the respiratory cycle.[5] The HR and its beat-to-beat variations are dependent on the rate of discharge of the primary pacemaker, the sinoatrial node, which is influenced by autonomic activities that are controlled in a complex way by a variety of reflexes. This discharge is largely controlled by parasympathetic (vagal) influence. So, HRV is influenced mostly by vagal activity. Recently HRV has been proposed as the most sensitive indicator of autonomic functions especially for the assessment of sympathovagal balance. During its sub-clinical phase, HRV is influenced by the balance between parasympathetic and sympathetic tones and can help in detecting CAN before the disease is symptomatic. Reduced heart rate variation is the earliest indicator of CAN.[6]

There are not many studies which have used HRV as the single diagnostic tool to assess CAN in diabetic patients preoperatively and to predict the hemodynamic instability under general anaesthesia (GA). Hence, this study is being conducted to define the possible role of HRV as a sole screening tool for detection of CAN in diabetic patients, to aid in optimal management of cardiovascular complications which can occur during induction of GA. We hypothesized that preoperative HRV can guide in selecting individuals who need further cardiac evaluation for optimization prior to surgery.

2. Materials and Methods

This cross- sectional study was conducted at a tertiary care health centre based in Bangalore, India during February 2018 to November 2019, after approval by the institutional review board.

The study was conducted in accordance with the declaration of Helsinki throughout the project. Informed consent was obtained from all the patients in the study.

The primary objective was to assess and compare the autonomic function using HRV in diabetic and non-diabetic patients preoperatively. The secondary objective was to study the hemodynamic responses of these patients during induction of GA. We included patients aged between 30 to 65 years, American society of anaesthesiologists (ASA) physical status 1 and 2, elective surgeries posted under GA, type 2 DM on treatment optimized to random blood sugar (RBS)< 200 mg/dL with duration of diabetes of less than 5 years and body mass index (BMI)< 30. We excluded patients who are athletes, with HR< 50 beats per minute, history of substance abuse, patients with cardiovascular/ respiratory/cerebrovascular disorders, individuals on beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, medications affecting ANS and patients with anticipated difficult airway.

Sample size was calculated based on the study conducted by Huang et al.[7] on pre-operative measurement of HRV predicting hypotension during GA, showing significant difference in hypotension between diabetics and non-diabetics (30% vs 7%). Expecting a similar result, our study required a total minimum sample size of 68 to achieve power of 80% and alpha error of 10% at 95% confidence interval (after adjusting for lost to follow-up, drop-out rate, and non-response rate). Based on this, 34 patients each were analysed in diabetics (Group D) and non-diabetics (group N).

The patients underwent HRV testing for 10 minutes (after resting for 10 minutes with eyes open during recording) on the previous day of surgery with power lab 15T lab chart hardware and software by ADInstrument (ADInstruments Ltd UK) (Figure 2). Lead II ECG was used for recording and HRV was analysed. In HRV measurement, the time domain variables analysed were SDNN (square root of variance), RMSSD (Square root of mean of the sum of the squares of difference between adjacent NN intervals) and NN50 (the square root of mean squared difference of successive NN intervals). Frequency domain variables studied were TP (Total power), LF (low frequency) power, HF (high frequency) power and LF/HF ratio.

On the day of surgery, in the pre-operative room all patients were preloaded with 500ml of ringer's lactate and shifted to the operation theatre. ASA standard monitors were connected and baseline vitals was recorded. Blood sugars were recorded before induction using a glucometer (Accu check Active blood glucose monitoring system). Patients were pre-oxygenated for 3 minutes with 100% oxygen. Induction of anaesthesia was standardized for all patients with IV fentanyl 2mcg/kg, propofol dose was titrated to loss of response to verbal commands (administered over 30 to 60 seconds) and muscle relaxation with vecuronium 0.1 mg/kg. This was followed by mask ventilation and endotracheal intubation was done with appropriate sized cuffed endotracheal tube, positive pressure ventilation was adjusted to end-tidal carbon dioxide of 28 to 32mm Hg and peak airway pressures of < 25cm of H2O with PEEP of 5cm of H2O. Patients were maintained on O2/N20 (50: 50) and sevoflurane was titrated to MAC (Minimum alveolar concentration) 1.0. All intubations were performed by the consultant anaesthesiologists.

The heart rate, the systolic, diastolic & mean arterial pressure (MAP) were recorded at preinduction, postinduction, postintubation and for every 3minutes thereafter for 15 minutes. Hypotension was defined as MAP <60 mm Hg or MAP <20% of baseline and bradycardia was defined as HR <50 beats per minute or <20% from baseline. Hypotension & bradycardia were treated with ephedrine 6mg and atropine 0.6mg boluses respectively.

Statistical analysis was performed using SPSS 22.0 and R environment ver.3.2.2. Normally distributed quantitative variables were described as mean and standard deviation, non-normally distributed quantitative variables as median and range, and qualitative variables as a percentage. All the quantitative variables like age, weight, height, BMI was summarized using descriptive statistics. Gender distribution in both groups were matched with chi square test. The height, weight and body mass index in both diabetics and non-diabetics were compared by student paired t test. P value ≤0.05 was considered significant.

3. Results

In the present study, a total of 90 patients were assessed for eligibility, out of which 68 patients had completed the trial successfully and their data were analysed as per protocol (Figure 1). The demographic data of age, gender, height, weight and BMI were comparable across both the groups (Table 1). In group D, the baseline blood sugars before induction varied from 156 to 189 mg/dl.

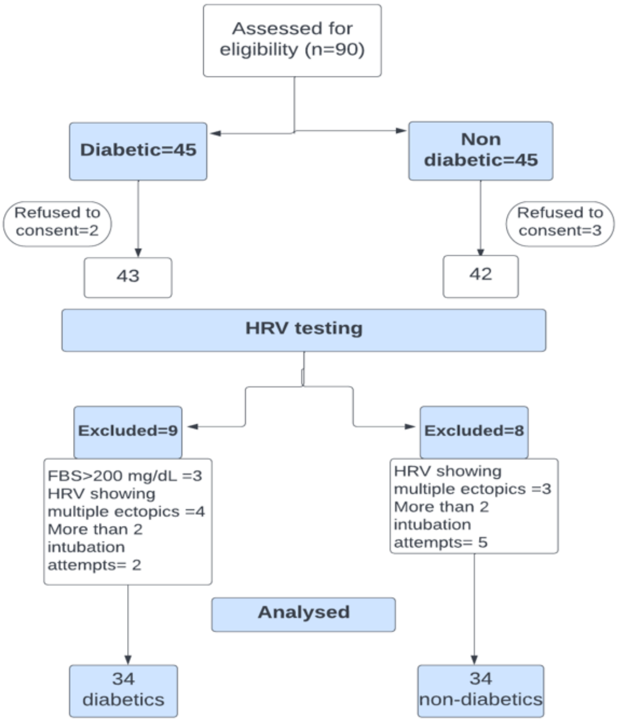

Figure 1: Patient allocation details

For HRV analysis, mean of time domain measures-SDNN and RMSSD were calculated and analysed. SDDN and RMSSD were observed to be higher in diabetic group compared to non-diabetic group however the difference was not statistically significant. In frequency domain analysis, TP was significantly lower in diabetic group. However, HF power, LF power and LF/HF were comparable (Table 2).

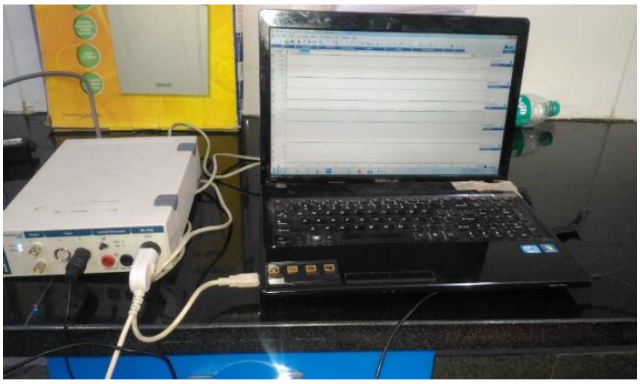

Figure 2: Trend of heart rate (HR) in diabetics & non-diabetics

The intraoperative HR trend in diabetics and non-diabetics were comparable (Figure 3). The diabetics had an increased predisposition to develop bradycardia. The post induction HR decrease was higher in group D as compared to group N (p= 0.06). Lower trend in MAP was observed in both groups after induction (Table 3). The diabetics had comparatively lower MAP compared to non-diabetics especially post induction, post intubation and the difference was significant 12min post-intubation (p= 0.04). Accordingly, the ephedrine usage was observed more in diabetics (p= 0.07).

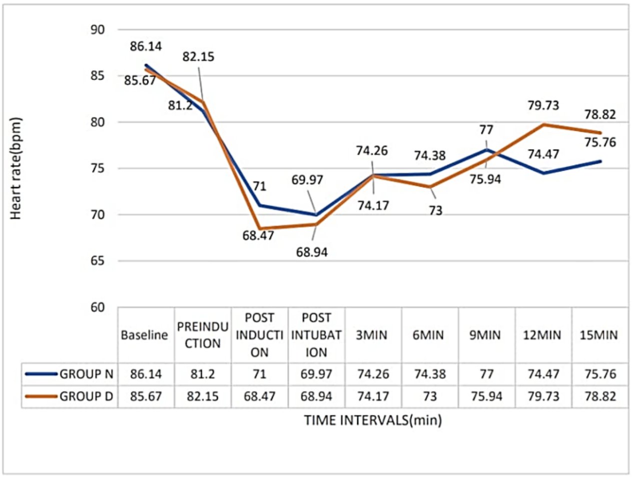

Figure 3: Trend of HR in diabetics & non-diabetics

4. Discussion

We conducted a cross- sectional study, to pre-operatively assess type 2 diabetics of less than 5 years duration for

Table 1: Demographic data (p value <0.05 was considered significant)

Parameter	Group N	Group D	p value
Mean age +/- SD (in years)	43.32 ± 15.63	43.58 ± 17.40	0.47
Males/ females	18/16	14/20	0.25
BMI (Mean ± SD in kg/m2)	23.29 ± 2.50	23.28 ± 3.12	0.49

Table 2: Mean time & frequency domains of HRV (p value <0.05 was considered significant)

Variable	Group N	Group D	P Value
SDNN (in ms)	146.09 ± 58.97	150.09 ± 69.48	0.38
RMSSD (in ms)	78.00 ± 106.17	84.29 ± 128.26	0.38
Total power (in ms^2)	2606.38 ± 1120.75	1721.05 ± 1315.76	0.003*
Low frequency power (in ms^2)	950.01 ± 679.21	940.11 ± 597.86	0.48
High frequency power (in ms^2)	930.28 ± 1068.94	940.69 ± 450.16	0.34
Low frequency power (normalized units)	43.50 ± 12.35	40.71 ± 18.25	0.20
High frequency power (normalized units)	34.51 ± 9.44	37.73 ± 13.93	0.13
LF/HF ratio	1.21	1.15	0.27

Table 3: Trend in MAP between the groups

Variable	Group N	Group D	P Value
Baseline MAP	89.79	92.82	0.06
Preinduction MAP	84.26	86	0.20
Postinduction MAP	73.09	73.2	0.47
Postintubation MAP	70.18	72.67	0.14
3 min MAP	75.08	76	0.30
6 min MAP	77.08	75.17	0.12
9 min MAP	77.29	75.94	0.25
12 min MAP	77.97	74.7	0.04*

HRV and to evaluate their hemodynamic fluctuations during induction of GA. This study was conducted to define the possible role of HRV as a sole screening tool for detection of CAN in short term diabetic patients to aid in optimal management of cardiovascular complications which can occur during GA. Studies using HRV in a larger population have demonstrated impaired HRV as reported in our study. However, data on Indian diabetic patients and their autonomic changes are very limited.

Diabetic autonomic neuropathy is among the least recognized and understood complications of diabetes and is associated with increased morbidity and mortality.[6] The risk of developing autonomic dysfunction in DM depends on duration of the disease and the degree of glycaemic control. The precise aetiology and pathologic mechanisms of diabetic autonomic neuropathy remain unclear and is proposed to be multifactorial. The polyol pathway activation leading to increased sorbitol accumulation, autoimmunity and oxidative stress are some of the etiological causes attributed. Disturbed regulation of blood flow may also play a role in the etiopathogenesis. The American Diabetes association recommends screening for distal symmetric neuropathy beginning with the initial diagnosis of diabetes and screening for autonomic neuropathy 5 years after diagnosis of type 1 DM and at the time of diagnosis of type 2 DM. All individuals with diabetes should then be screened annually for both forms of neuropathy.[8]

We screened 68 subjects (diabetics and non-diabetics in 1:1 ratio) with comparable demographic data, by short term HRV recording (for 10 minutes) and analysed both time and frequency domain analysis. It was demonstrated in our study that the TP is significantly lower in diabetics. Diabetics with lower TP had an increased predisposition for hypotension compared to the control group. The decreased TP also correlated with the post intubation hypotension at 12^{th} minute (p= 0.04). In our study the lower TP <500 ms^2 had more propensity to predict intra-operative hypotension. Huang et al.[7] found similar correlation in diabetic patients with HRV deviation and intraoperative hypotension. They concluded TP as an independent predictor of hypotension during GA. They found that LF, HF and TP were significantly lower in individuals who required intra-operative vasopressors compared to those who didn't. Similarly, A T Mazzeo et al.[5] reviewed many studies on HRV as a diagnostic and prognostic tool in anaesthesia and intensive care units demonstrating significantly lower HF, LF and total HRV in diabetic population.

Benichou et al.[9] evaluated HRV in diabetics and concluded that all the HRV parameters like RMSSD, SDNN, TP, HF power and LF power are lowered when compared to normal individuals. This suggests that there is overall decline in the autonomic activity with both sympathetic and parasympathetic activity getting affected. However, in our study, a statistically significant difference was noted in the diabetes group inferring decline in the autonomic activity even in short term diabetics. We also noted that there was a decrease in the HF power in the diabetics which is indicative of the decrease in the parasympathetic component rather than the overall activity. The efferent vagal activity is a major contributor to the HF component, as seen in clinical and experimental observations of autonomic manoeuvres such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy.[10,11] Parasympathetic activity is mainly affected due to low grade inflammation in early diabetes and prediabetic patients.[12]

Since we did not find much difference in LF power between diabetics and normal individuals, the overall sympathetic activity does not seem to be affected. This may be due to the fact that we recruited short term diabetics with RBS <200mg/dl on treatment with duration of diabetes of less than 5 years.

A prospective clinical study by Hanss et al.[13] investigated the value of HRV for prediction of hypotension and bradycardia after induction of GA in high-risk patients, defined by revised cardiac risk index score= 3. It was concluded that unstable patients had significantly lower baseline TP (TP < $500 ms^2 Hz^{-1}$) predisposing to post-induction hypotension or bradycardia.

A study by Kudat et al.[14] evaluated diabetic patients with chronic complications and showed that all time- and frequency-domain parameters except mean R– R interval (NN) and LF/HF were significantly lower when compared to diabetics without complications. They did not find any statistically significant difference in haemoglobin A1c (HbA1c) levels between diabetes patients with and without complications. However, a study done by Eller et al.[15] revealed negative association between TP & HF with both waist-to-hip ratio & HbA1c.

Our study has immense clinical relevance in preoperative evaluation of diabetic patients and in identifying patients susceptible for hypotension following GA in such population. We used HRV as a sole screening test for detection of autonomic dysfunction and the TP component was found to be a predictor of hypotension post anaesthesia induction.

This study has a few limitations. The cross- sectional nature of this study necessitates randomized control trials involving larger population to further validate the findings. The HRV was done only the day previous to surgery. In addition to pre-operative HRV, the HRV recordings in the intra-operative & post-operative period could been more informative. We also advise inclusion of other tests of autonomic function to assess CAN. In our view, HRV should be incorporated as a routine preoperative testing tool in diabetic patients.

5. Conclusion

The measurement of HRV is a simple bedside, non-invasive, low-cost monitoring tool to evaluate the peri-operative risks in patients with suspected autonomic dysfunction, especially in short term diabetics. The TP may be a suitable variable to detect patients at high risk for cardiovascular instability and this might necessitate the need for intensified monitoring and prophylactic use of inotropes or vasopressors.

6. Conflict of Interest

Nil.

7. Source of Funding

Nil.

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Cite this article: Dinesh N, Lakshminarasimhaiah G, Kumar A, Musti S, Rao R, Khavas AS. Pre-operative screening of diabetic patients for heart rate variability and their hemodynamic responses during induction of general anaesthesia. *Indian J Clin Anaesth* 2023;10(4):334-339.