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Original Research

Cardiac Autonomic Neuropathy: Comparative performance of Phase-Rectified Signal Averaging methods with Cardiac Autonomic Reflex Tests and Time Domain Heart rate variability.

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Abstract

Background: Phase-Rectified Signal Averaging (PRSA) methods, Deceleration (DC), and Acceleration Capacity (AC), provide a comprehensive assessment of cardiac autonomic function (CAN). There are no published studies comparing PRSA methods with conventional methods such as Time Domain Heart Rate Variability (TD-HRV) or Cardiac Autonomic Reflex Tests (CARTs), nor have they described a cut-off value for AC and DC to distinguish patients with CAN (+ve) from those without CAN (-ve). Our study compares PRSA methods with conventional methods and defines cut-off values for AC and DC to diagnose CAN.
Methodology: We studied two cohorts: 126 individuals with normal ventricular function (derivation cohort) and 143 individuals with Left Ventricular Dysfunction (validation cohort). These patients underwent CARTs and supine, resting ECG recordings for 2 to 3 minutes. The patients were categorized as CAN +Ve and CAN -Ve based on TD-HRV parameters and the CARTs. Two different CART criteria were studied: the All-India Institute of Medical Sciences (AIIMS-AFT) criteria and the 2011 Toronto Consensus recommendations. Patients with and without CAN were segregated by AC and DC values, and the methods were compared. The cutoff values for DC and AC were calculated using the ROC curve method from the derivation cohort and verified in the validation cohort.
Results: A reduction in DC values and an increase in AC values indicate a higher chance of CAN. The cut-off values of -7 for AC and 7 for DC provide the highest accuracy in detecting CAN prevalence. Both values have an AUC of nearly 0.9. Reclassifying both Cohorts as CAN +Ve based on the derived cut-offs and comparing with the prevalence determined by conventional methods results in kappa values ranging from 0.5 to 0.7.
Conclusions: A decrease in DC value and an increase in AC value are associated with a higher probability of CAN. An AC value ≥ -7 and a DC value ≤ 7 indicate good accuracy in identifying CAN.

Keywords: Cardiac Autonomic Function, Phase-Rectified Signal Averaging, Deceleration capacity, Acceleration capacity, Heart Rate Variability, Cardiac Autonomic Reflex Tests.

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Quick Response Code:

Introduction

In 2006, Axel Bauer et al. [1] described the RR interval processing technique, phase-rectified signal averaging (PRSA), to calculate the Deceleration capacity (DC) and Acceleration capacity (AC). After 2006, multiple studies on DC and AC in different patient groups, such as diabetes [2], heart failure [3,4], stroke [5], and other conditions [6,7], have been published.

These studies have confirmed the utility of PRSA methods for CAN evaluation; however, no studies have compared them with conventional methods such as TD-HRV or gold-standard CARTs.

The present study assesses the comparative performance of both PRSA methods, DC and AC, with conventional common method TD-HRV and the 'gold standard' CARTs in two different populations, those with normal Left Ventricular function (NLV) and those with left ventricular dysfunction (LVD). The cutoff values for DC and AC to define CAN +Ve are determined using the ROC curves.

Though 24-hour ECG recordings are the norm for PRSA analysis, few studies used short- duration ECG recordings such as 30 minutes [8] and 5 minutes [9]. We used ultra-short-duration recordings (2-3 minutes) for DC and AC calculations. This reduction in ECG recording duration represents a paradigm shift, as DC and AC calculations become simpler, reducing patient burden and cost.

Standard and non-standard abbreviations.

PRSA-Phase Rectified Signal Averaging, AC: Acceleration Capacity, DC: Deceleration Capacity.

Aims of the study.

To assess the comparative performance of AC and DC with Time-Domain Heart Rate Variability (TD-HRV) and Cardiac Autonomic Reflex Tests (CARTs) in detecting the prevalence of Cardiac Autonomic Neuropathy (CAN).

Methods

This study was conducted in accordance with the Declaration of Helsinki. The institutional ethics committee (Little Flower Hospital and Research Centre, Angamaly, Kerala) approved the CAN-HF study protocol (EC/01/2023) on 29.03.2023. This analysis is based on data from the CAN-HF study.

The study was conducted at Little Flower Hospital and Research Centre, Angamaly, Kerala, and the recruitment period was from 01.09.2023 to 31.03.2025. The study included two cohorts: first, healthy individuals aged 30 to 75 years with normal ventricular function and no structural heart disease, who underwent radial coronary angiography for various reasons. In this cohort, patients with a prior history of acute coronary syndrome and >50 % epicardial coronary artery disease were excluded. The second cohort included patients with Left Ventricular dysfunction irrespective of coronary artery disease. They were recruited based on a recent (< 1 month) Echocardiographic report with an Ejection Fraction <50% or an Average Global Longitudinal Strain (GLS) <16%. All consecutive patients were recruited after providing written informed consent. Patients with seizure disorder, neurodegenerative diseases, eGFR <30 mL/mt/1.73m^2, and chronic pulmonary disease were excluded.

Data collection.

After obtaining written informed consent, the study team trained participants in performing each component of the CARTs. After the initial training and rest period, ECG and blood pressure data were recorded for two to three minutes on a Philips Intellivue MP20-MP90 monitor. The Medicollector software (MediCollector Inc., Boston, MA, United States) [10] captured the ECG signals at 500 Hz, and the blood pressure signals at 125 Hz, and transferred the data to Excel format. If data quality was not satisfactory, repeat sampling was performed until a high-quality trace was obtained. We developed two dedicated software programs: one to detect 'NN' intervals and another to calculate AC and DC. The detailed

descriptions are given in Supplementary file -1. The steps for calculating AC and DC are as described by Axel Bauer [1], but instead of a 24-hour ECG recording, we used ultra-short-duration ECG data (2-3 minutes). After validating both the software in an adequate number of trial runs, we used them in the study. The ECG recordings at 500 Hz provided this protocol with 2-millisecond precision. After procuring clean baseline tracings, the cardiovagal tests were performed.

Data cleaning and editing.

The electronic data in Excel format was spread as ECG complexes and visually inspected. Non-sinus beats, or artifacts, were edited by appropriate methods as described, either by deletions or interpolations [11,12]. Interpolation was used to edit premature atrial and ventricular complexes. Repeat sampling for artifact-free data reduced the need for editing, with <1% of complexes requiring editing, which is significantly lower than the standard recommendation of 20% or less [13].

Three CAN definitions were used to assess the prevalence of CAN. Two are CART definitions, both being modifications of Ewing's original criteria [14]: 1) Toronto Consensus Panel recommendations on Diabetic Neuropathy (2011) [15], and 2) All India Institute of Medical Science- Autonomic Function Test laboratory criteria (AIIMS-AFT) [16]. The CART manoeuvres were performed per the recommendations of the Diabetic Neuropathy Study Group of the Italian Society of Diabetology [17]. The third definition was based on TD-HRV. The age-specific cutoff value published by Andreas Voss [18] is used as the reference value. (Review of the three criteria in Supplementary file - 2).

Both cohorts were analysed for CAN using the three criteria, and median AC and DC values were calculated for those with and without CAN. A cutoff value for AC and DC to discriminate CAN + Ve was obtained from the derivation cohort (patients with normal LV function), and this value was verified in the validation cohort (patients with LV Dysfunction).

Statistical analysis.

Statistical analyses were conducted using SPSS Version 20.0 for Windows (IBM Corporation, ARMONK, NY, USA). Categorical variables were presented as numbers and percentages, and continuous variables as medians and interquartile ranges (IQRs). The Mann-Whitney test was used to compare AC and DC values between the two cohorts and subgroups. The receiver operating characteristic (ROC) curve method was used to determine the cutoff values of AC and DC for the CAN +ve and CAN-ve groups, and to calculate the area under the curve (AUC). An interrater reliability analysis using the Kappa statistic was performed to determine consistency among criteria. Sensitivity, Specificity, Positive Predictive value, Negative Predictive value, False positive rate, False negative rate, and Accuracy were calculated.

Results

309 individuals consented to participate in the study. After elimination of poor ECG tracings, poor participant cooperation during different study manoeuvres, and incomplete data, 126 participants' data were available for analysis in the derivation cohort and 143 in the validation cohort.

The participants were adults and seniors aged 32-75 years, with a mean (± SD) age of 55.9 ± 8.5 years for those with normal LV function and 58.3 ± 9 years for those with LV dysfunction. The majority in the normal LV function group were females (69.8%), while males predominated (74.1%) in the LV dysfunction group. Supplementary file - 3 shows the demographic profile of participants.

The CAN prevalence varied according to different criteria. Patients with LV dysfunction had a higher prevalence of CAN across all criteria (Table 1). CAN prevalence determined by AIIMS criteria is the most specific, while that by Toronto-2011 is the most sensitive.

Criteria Studied	***Cohort-1 (126 participants with Normal LV Function)***			***Cohort-2 (143 participants with LV Dysfunction)***		
	Definite pCAN	Early pCAN	Total pCAN	Definite pCAN	Early pCAN	Total pCAN
Toronto 2011	22 (17.5)	21 (16.7)	43 (34.2)	48 (34.5)	40 (28.8)	88(63.3)
AIIMS	3 (2.4)	24 (19.0)	27 (21.4)	19 (14.1)	35 (25.9)	54 (40)
HRV			38 (30.2)			74 (51.7)

Table 1: CAN prevalence by different criteria. pCAN- parasympathetic cardiac autonomic Neuropathy.

Median values of AC and DC in two cohorts.

CAN+ve patients have higher AC and lower DC values than those without (Supplementary file – 2, Tables S2 and S3). The median AC values were higher, and the median DC values were lower in the LV dysfunction cohort compared with those with normal LV function; this difference persisted in the CAN -Ve patients but was not statistically significant in the CAN +Ve patients when analysed by CARTs (Table 2, marked *).

	Criteria	Normal LV Function Median (IQR)	LV Dysfunction (Validation) Median (IQR)	P value
AC	Overall	-8.62 (-12.90, -5.44)	-5.20 (-7.89, -3.13)	<0.001
	Toronto-CAN -Ve	-10.41 (-14.73, -7.25)	-7.48 (-11.45, -5.60)	0.002
	AIIMS CAN -Ve	-9.46 (-13.99, -6.10)	-7.10 (-10.83, -4.63)	0.001
	HRV CAN -Ve	-9.80 (-14.61, -7.32)	-7.25 (-11.31, -5.67)	0.001
	Toronto CAN +Ve	-5.23 (-6.64, -3.00)	-3.99 (-6.57, -2.60)	0.159 *
	AIIMS CAN + Ve	-4.81 (-6.70, -3.00)	-3.58 (-5.29, -2.21)	0.046 *
	HRV CAN +Ve	-5.27 (-6.07, -3.28)	-3.64 (-5.14, -2.24)	0.003
DC	Overall	8.25 (5.19, 11.77)	5.57 (3.18, 7.68)	<0.001
	Toronto-CAN -Ve	10.23 (7.69, 14.28)	7.43 (5.87, 12.05)	0.006
	AIIMS CAN -Ve	9.25 (6.26, 13.72)	7.05 (4.98, 9.91)	0.001
	HRV CAN -Ve	9.90 (7.81,14.24)	7.43 (5.86, 11.70)	0.002
	Toronto CAN +Ve	4.66 (3.25, 6.26)	4.07 (2.67, 6.28)	0.301 *

	AIIMS CAN + Ve	4.46 (3.06, 5.81)	3.57 (2.38, 5.48)	0.123 *
	HRV CAN +Ve	4.94 (3.25, 5.77)	3.55 (2.40,5.48)	0.015

Table 2. Median value comparison between two cohorts, in those with and without CAN.

Segregation of CAN +ve based on AC and DC values.

Patients with CAN +ve and CAN -ve were segregated against each AC and DC value. (Patients segregated against each AC and DC values, and CAN +ve and CAN -ve patients against AC/DC values are shown in supplementary file-4). The Positive Predictive Value (PPV) of CAN increases with a reduction in DC values and an increase in AC values. Almost all patients with AC values > -3 and DC values <3 have CAN.

Cut-off values for AC and DC: Based on the CAN prevalence data using the above three criteria, cut-off values for AC and DC are derived using the ROC curve method (Table 3).

Basic Criteria	**Cut off value**	**Sensitivity**	**Specificity**	**AUC (95% CI)**	**p-value**
Acceleration Capacity					
Toronto 2011	-6.740	81.4%	79.5%	0.898 (0.844-0.951)	<0.001
AIIMS	-7.940	92.6%	64.6%	0.841 (0.765-0.917)	<0.001
HRV	-6.715	89.5%	80.7%	0.887 (0.829-0.945)	<0.001
Deceleration Capacity					
Toronto 2011	7.285	77.1%	83.7%	0.901 (0.847-0.956)	<0.001
AIIMS	7.935	65.7%	96.3%	0.864 (0.791-0.937)	<0.001
HRV	7.285	78.4%	94.7%	0.910 (0.859-0.960)	<0.001

Table 3: Cutoff values for AC and DC. The receiver operating characteristic (ROC) curve method is used to detect the cut - off values and the area under the curve (AUC).

The cutoff values varied across criteria, and all had high AUCs (around 0.9). (ROC curve graphs in Supplementary file 5). When rounded to the nearest whole number, the cutoff values for AC were -7 and -8, and for DC, they were 7 and 8. The AC cut-off values showed high sensitivity, while the DC cut-off values showed high specificity.

Validation of the AC and DC cut-off values:

The newly derived cut-off values were used to reclassify both the cohorts as CAN +ve and CAN -ve. The prevalence is given in Supplementary file 2, Table S1. The prevalence of CAN, determined by AC and DC values, was validated against the three conventional CAN criteria mentioned (HRV- based, Toronto-2011, and AIIMS criteria). The accuracy of the new classification for both cohorts is shown in Table 4, and the intertest agreement in the LV dysfunction Cohort is shown in Table-5. The accuracy and intertest agreement were marginally better for the AC value of -7 and DC value 7.

Basic Criteria	**AC-7**	**AC-8**		**DC 7**	**DC 8**
Normal LV Function (Cohort-1)					
Toronto-2011	78.6 %	78.6 %		78.6 %	80.2 %
AIIMS	70.6 %	70.6 %		73.8 %	70.6 %
HRV	81.0 %	81.0 %		84.1 %	79.4 %
Average Accuracy	76.73 %	76.73 %		78.83 %	76.73 %
LV Dysfunction (Cohort-2)					
Toronto-201	74.1 %	73.4 %		77.7 %	73.4 %
AIIMS	68.9 %	62.2 %		66.7 %	59.3 %
HRV	74.8 %	71.3 %		76.9 %	69.9 %
Average Accuracy	72.6%	69 %		73.8%	67.5%

Table 4. Accuracy comparison of different cut-off values.

Criteria	**AC-7** **Kappa** **(P value)**	**DC 7** **Kappa** **(P value)**	**AC-8** **Kappa** **(P value)**	**DC 8** **Kappa** **(P value)**
Toronto (Total pCAN)	0.433 (<0.001)	0.510 (<0.001)	0.378 (<0.001)	0.367 (<0.001)
AIIMS (Total pCAN)	0.413 (<0.001)	0.373 (<0.001)	0.316 (<0.001)	0.271 (<0.001)
HRV	0.491 (<0.001)	0.533 (<0.001)	0.416 (<0.001)	0.386 (<0.001)

Table-5. Inter-test agreement (kappa values) of CAN prevalence by the AC/DC cut-off values in the LV dysfunction Cohort.

Discussion

The Acceleration and Deceleration capacity give an overall impact of autonomic influence [19] and are early indicators of autonomic imbalance [20].

Following the publication of the foundational study on AC and DC by Axel Bauer et al. in 2006, multiple studies have examined the utility of AC and DC in various disease conditions [1,2,3,4,5,7,8,20,21,22,23,24,25,26,27] (Supplementary Table S3). No studies have compared the validity of PRSA methods AC and DC with conventional TD-HRV or CARTs.

CAN is a progressive disorder; all markers of this pathophysiology behave as continuous variables and are considered abnormal when they exceed specific cut-off values. There are multiple diagnostic criteria for CAN that evaluate different physiologic aspects [15]. Different criteria are considered complementary rather than mutually exclusive in diagnosing CAN [15]. CARTs, the 'gold standard' specific criteria, are based on a set of manoeuvres and diagnose CAN at a later definitive stage, while HRV is an early marker [28].

Both cohorts in the study have a higher prevalence of risk factors for CAN, which accounts for the higher prevalence of CAN across all criteria. Both AC and DC are indices of Heart Rate variability, so a lower absolute numerical value means lower Heart rate variability. As AC has negative values, higher values are abnormal, while lower values are abnormal in the Deceleration capacity.

PRSA methods are earlier markers of CAN.

The median AC values were higher, and the median DC values were lower in the LV Dysfunction cohort compared to the NLV cohort. In the subcategory analysis based on CARTs, these variations remained significant in the CAN -Ve patients but became insignificant in CAN +Ve patients. As markers of CAN, higher AC values and lower DC values are expected in CAN +Ve patients. Given that LV dysfunction is a strong predictor of CAN development, higher AC and lower DC values are expected in patients with LV dysfunction. CARTs diagnose CAN at a later, more definitive stage, by which time AC and DC values have dropped so low that differences between groups are no longer apparent. In the cohort with a higher risk of CAN (LV Dysfunction cohort), patients with CAN-negative results by traditional CARTs have higher median AC values and lower median DC values. This demonstrates that AC and DC are sensitive, early markers of CAN, identifying dysfunction before conventional CARTs.

PRSA methods and conventional methods.

The PRSA methods have been validated as a risk stratification tool; the data show that Deceleration Capacity (DC) is more robust than Acceleration Capacity (AC) [1,24,25]. In the LV dysfunction cohort, the 25th percentile value for DC in those with CAN is ≈ 2.5 (varies from 2.38 to 2.67), and the 75th percentile value for AC is ≈ -2.5 (varies from -2.21 to -2.6). The 25th percentile value for DC corresponds to the high-risk category (DC ≤ 2.4), as described by Axel Bauer [1].

In both cohorts, segregation of CAN+ve and CAN-ve patients based on AC and DC values confirms that as DC values decrease and AC values increase, the PPV of CAN increases, but at the expense of reduced sensitivity. Almost all patients with AC values > -3 and DC values <3 have CAN, but these low cut-off values have low sensitivity and miss the majority of patients with CAN diagnosed by any CART or HRV criteria.

Ultra-short duration ECG recordings for PRSA methods.

Studies have validated ultra-short-duration (<5 minutes) ECG recordings for TD-HRV analysis. Most of the PRSA studies used 24-hour recordings; however, short-duration recordings have also been validated [8,9]. In the KORA-KMC study, a 5-minute recording was analysed [9]. The expected pattern of AC and DC value variation between normal LV function and those with LV Dysfunction, and between CAN +Ve and CAN -Ve patients, in the present study validates that ultra-short-duration ECG recordings are feasible for evaluating AC and DC values. The reduction in ECG recording duration represents a paradigm shift, as DC and AC calculations become simpler, thereby improving editing accuracy, reducing patient burden, and lowering costs. Consequently, DC and AC become valuable CAN testing tools for large-scale population-based studies and for routine clinical practice.

Cut-off values for PRSA methods to diagnose CAN.

The literature search does not identify a study that defines AC and DC cutoff values to discriminate CAN+ve patients from the -ve population. The cutoff values obtained in the present analysis showed only marginal variation across criteria, and all had high AUCs (around 0.9). Both the cutoff values were validated by assessing accuracy and intertest agreement. They showed an overall accuracy ≈ 70% in both cohorts, but it was marginally higher for an AC value of -7 and a DC value of 7. In the analysis of intertest agreement in the validation cohort, the cut-off values of -7 for AC and 7 for DC performed better, though the agreement was only moderately strong (maximum kappa value = 0.533). The segregation graph shows that, at this cutoff value, there are significant false positives when analyzed by conventional methods. The conventional methods of CAN detection and PRSA methods analyse different aspects of CAN, which explains the relatively poor correlation between tests.

Existing knowledge indicates that PRSA methods are markers of CAN and valid tools for risk stratification. The present study establishes PRSA as a tool for assessing CAN prevalence by defining a cutoff value.

Conclusions

Alterations in AC and DC are earlier markers of Cardiac Autonomic Neuropathy than CARTs. The prevalence of CAN determined by PRSA methods is not directly comparable to that identified by conventional methods such as TD-HRV and CARTs. A decrease in DC value and an increase in AC value are associated with a higher probability of CAN. An AC value ≥ -7 and a DC value ≤ 7 demonstrates good accuracy in identifying CAN. However, the prevalence identified with these cut-off values shows only moderate intertest agreement with conventional methods.

Limitations of the study.

It is a single-center study.

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