

# Low deceleration capacity is associated with higher stroke risk in patients with paroxysmal atrial fibrillation

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## Abstract

**Background:** Deceleration capacity (DC) is a non-invasive marker for cardiac autonomic dysfunction; however, few studies have shown that the influence factors of cardiac autonomic dysfunction and the correlations between DC and stroke risk in paroxysmal atrial fibrillation (AF). We aimed to explore the influencing factors of abnormal DC and the relationships between DC and stroke risk in patients with paroxysmal AF.

**Methods:** The study included hospitalized paroxysmal AF patients with DC measurements derived from 24-h Holter electrocardiography recordings taken between August 2015 and June 2016. Multivariable regression analysis was performed to evaluate the associations between correlated variables and abnormal DC values. The relationship between DC and ischemic stroke risk scores in patients with paroxysmal AF was analyzed.

**Results:** We studied 259 hospitalized patients with paroxysmal AF (143 [55.2%] male, mean age  $66.4 \pm 12.0$  years); 38 patients of them showed abnormal DC values. In the univariate analysis, age, hypertension, heart failure, and previous stroke/transient ischemic attack (TIA) were significantly associated with abnormal DC values. Among these factors, a history of previous stroke/TIA (odds ratio = 2.861, 95% confidence interval: 1.356–6.039) were independently associated with abnormal DC values in patients with paroxysmal AF. The abnormal DC group showed a higher stroke risk with the score of congestive heart failure, hypertension, age >75 years, diabetes mellitus, previous stroke and TIA (CHADS<sub>2</sub>) ( $2.25 \pm 1.48$  vs.  $1.40 \pm 1.34$ ,  $t = -4.907$ ,  $P = 0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-vascular disease, age 65–74 years and female category (VASc) ( $3.76 \pm 1.95$  vs.  $2.71 \pm 1.87$ ,  $t = -4.847$ ,  $P = 0.001$ ) scores. Correlation analysis showed that DC was negatively correlated with CHADS<sub>2</sub> scores ( $r = -0.290$ ,  $P < 0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ( $r = -0.263$ ,  $P < 0.001$ ).

**Conclusions:** Lower DC is closely associated with previous stroke/TIA, and is also correlated negatively with higher stroke risk scores in patients with paroxysmal AF. It could be a potential indicator of stroke risk in paroxysmal AF patients.

**Keywords:** Deceleration capacity; Atrial fibrillation; Stroke; Cardiac autonomic

## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of ischemic stroke, heart failure, and mortality.<sup>[1]</sup> Stroke risk assessment of AF is currently mainly based on CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.<sup>[2]</sup> Both scores include known major risk factors, such as age, diabetes, heart failure, previous stroke/transient ischemic attack (TIA), and hypertension. AF is a complex type of arrhythmia and has multiple mechanisms. Its pathophysiology includes electrical remodeling, structural remodeling, and autonomic neural dysregulation.<sup>[3]</sup> The cardiac autonomic nerve system (CANS) is a potential trigger for and modulator of the initiation and maintenance of AF. Fluctuations in the

CANS are common before the onset of paroxysmal AF.<sup>[4]</sup> Furthermore, neuronal remodeling can lead to an abnormal release of neurotransmitters, thereby affecting the ion channel status and increasing AF susceptibility.

Deceleration capacity (DC) was first proposed in 2006<sup>[5]</sup> as a reliable non-invasive electrocardiographic index for the quantitative measurement of cardiac autonomic nervous tension.<sup>[6]</sup> DC has proven to be a superior indicator compared to heart rate variability, which has been traditionally used to assess cardiac autonomic function.<sup>[7]</sup> DC has been also confirmed to predict post-myocardial infarction sudden death better than left ventricular ejection fraction (LVEF) and standard deviations of all normal-to-normal intervals. A preserved DC (>4.5 ms) has been found to indicate an extremely low risk of mortality, whereas a

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poor DC ( $\leq 2.5$  ms) indicates a higher mortality risk.<sup>[5]</sup> DC has also been used to assess the effects of circumferential or segmental pulmonary vein ablation for paroxysmal AF on cardiac autonomic function.<sup>[8]</sup> In addition, the results of a study by Rademacher *et al* have shown that abnormally low DC values ( $< 4.5$  ms) indicated severe vagal insufficiency, which elucidated that DC may help to predict the recurrence of persistent AF after cardioversion.<sup>[9]</sup>

Therefore, this study was conducted to investigate the clinical characteristics and influencing factors of abnormal DC and to study the relationship between DC and stroke risk scores in patients with paroxysmal AF.

## Methods

### Ethical approval

The study and consent procedures were performed in accordance with the *Declaration of Helsinki*. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University. All patients had signed the informed consents.

### Study population

In this study, we consecutively included all patients with paroxysmal AF admitted to our hospital from August 1, 2015 to June 30, 2016. AF patients were defined as individuals with International Classification of Diseases, 10th Revision, Clinical Modification diagnostic codes of AF, confirmed by electrocardiography (ECG) or Holter monitor recordings in the inpatient setting. Paroxysmal AF is defined by episodes that last  $< 7$  days and terminate spontaneously.<sup>[10]</sup> The patients with paroxysmal AF were pre-screened prior to being included in this study, and those with valvular heart diseases or those who were included prior to the age of 18 years were excluded. For the study analyses, we excluded patients who had missing or invalid DC data on 24-h Holter ECG or who had missing data for important covariates. In order to ensure the validity and accuracy of Holter ECG parameters collection, patients without valid Holter ECG recordings (eg, a recording time less than 20 h or excessive noise) or not sinus rhythm during Holter ECG recording were also excluded.

### Data collection

The demographic and clinical characteristics of the included patients were extracted from the hospital information system used at our hospital. The following data were extracted: age, sex, weight, height, smoking status, blood pressure levels at admission, concomitant diseases, and echocardiographic parameters. Body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). We calculated the CHADS<sub>2</sub> score (one point each for congestive heart failure, hypertension, age older than 75 years, and diabetes, and two points for previous stroke/TIA/thromboembolism [TE]) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores (one point each for systolic heart failure, hypertension, age 65–74 years, diabetes, vascular disease, and female sex; and two points each for age older than 75 years and previous stroke/TIA/TE) to assess the

ischemic stroke risk in patients with paroxysmal AF. We performed risk stratification according to the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores: 0 point was classified as low risk, 1 point as medium risk, and  $\geq 2$  points as high risk.<sup>[11]</sup>

### Concomitant diseases and drug therapies

Concomitant diseases were extracted from patient medical notes and diagnoses. Hypertension was defined as an average systolic blood pressure  $\geq 140$  mmHg or an average diastolic blood pressure  $\geq 90$  mmHg.<sup>[12]</sup> Diabetes was defined as a fasting glucose level  $\geq 7.0$  mmol/L (or a non-fasting glucose level  $\geq 11.1$  mmol/L).<sup>[13]</sup> Heart failure was defined as the presence of signs and symptoms of right and/or left ventricular dysfunction, as confirmed by a LVEF value  $< 40\%$  by echocardiogram or a New York Heart Association (NYHA) classification worse than class II.<sup>[14]</sup> Coronary artery disease (CAD) was defined by self-reported history of myocardial infarction, coronary bypass, angiography, or ECG evidence of myocardial infarction. Any discrepancies were resolved by rechecking the medical records and through discussion by three researchers.

The drugs that might have an impact on DC that patients used during hospitalization are also collected. The types of drugs including  $\beta$ -blockers, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and amiodarone.<sup>[15]</sup>

### DC calculation

Cardiac autonomic function was measured using DC values. DC values were collected using a 12-lead Holter ECG recorder (BI9800TL, Biomedical Instruments Co., Ltd., Shenzhen, Guangdong, China) and analysis system (ECG Lab Holter Software, Biomedical Instruments Co., Ltd.). The calculation of DC values was based on the phase-rectified signal averaging method,<sup>[5]</sup> which was used to extract periodicities from complex time series. The DC values are presented in ms, and the lower limit for normal DC is 4.5 ms.

### Statistical analysis

For the statistical analyses, the sample size calculation for patients was done according to the previous study, using calculation method of difference test for comparison of two groups of rates. All parameters are reported as the mean  $\pm$  standard deviation. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables are presented as  $n$  (%) and were analyzed using Chi-square tests. Univariate and multivariate logistic regression analyses were performed to identify the risk factors associated with DC among the patients with paroxysmal AF. After performing the univariate regression analyses, variables with a  $P$  value  $< 0.05$  were selected as candidates for entry into the multivariate model. The variables selected for inclusion in the multivariable logistic regression model included age, hypertension, diabetes, and previous ischemic stroke/TIA. Correlations between DC with CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were calculated using the Spearman rank correlation test. Statistical data management was performed using Microsoft Excel (Microsoft Inc., California, USA), and statistical analyses were

**Table 1: Baseline clinical characteristics of the general study population.**

Clinical parameters	All patients (n = 259)	Normal DC group (n = 188)	Abnormal DC group (n = 71)	$\chi^2$	P
Demographic data					
Male Sex, n (%)	143 (55.2)	105 (55.8)	38 (53.5)	0.020	0.737
Age, mean $\pm$ SD (years)	66.4 $\pm$ 12.0	65.0 $\pm$ 12.0	70.2 $\pm$ 11.2	-2.945	0.002
<65 years, n (%)	101 (39.0)	85 (45.2)	16 (22.5)	9.028	0.004
65-74 years, n (%)	83 (32.0)	55 (29.2)	28 (39.4)		
$\geq$ 75 years, n (%)	75 (29.0)	48 (25.5)	27 (38.0)		
BMI, mean $\pm$ SD (kg/m <sup>2</sup> )	23.5 $\pm$ 3.3	23.4 $\pm$ 3.0	23.7 $\pm$ 4.1	-0.786	0.662
Blood pressure on admission					
SBP, mean $\pm$ SD (mmHg)	130.0 $\pm$ 19.2	129.2 $\pm$ 19.3	132.2 $\pm$ 18.9	-0.842	0.258
DBP, mean $\pm$ SD (mmHg)	74.5 $\pm$ 11.4	74.2 $\pm$ 10.6	75.4 $\pm$ 13.2	-0.071	0.445
Smoking, n (%)	71 (27.4)	57 (30.3)	14 (19.7)	3.546	0.088
Echocardiography, mean $\pm$ SD					
LVEF (mm)	60.3 $\pm$ 8.9	61.3 $\pm$ 8.1	57.7 $\pm$ 10.5	2.719	0.014
LVFS (%)	32.5 $\pm$ 6.0	33.2 $\pm$ 5.5	30.8 $\pm$ 6.9	2.746	0.014
LAD (mm)	36.3 $\pm$ 6.3	36.1 $\pm$ 6.4	37.0 $\pm$ 6.1	-1.529	0.333
AS (mm)	32.0 $\pm$ 3.3	32.0 $\pm$ 2.9	32.1 $\pm$ 4.1	-0.461	0.686
AVR (mm)	20.9 $\pm$ 1.7	20.9 $\pm$ 1.7	20.8 $\pm$ 1.8	0.910	0.633
AA (mm)	32.0 $\pm$ 3.4	32.0 $\pm$ 3.2	31.9 $\pm$ 3.7	0.210	0.918
RVAW (mm)	4.2 $\pm$ 0.6	4.2 $\pm$ 0.6	4.3 $\pm$ 0.6	-0.856	0.417
RVD (mm)	22.0 $\pm$ 2.9	22.0 $\pm$ 2.9	21.9 $\pm$ 2.7	-0.346	0.687
IVS (mm)	10.1 $\pm$ 1.5	10.1 $\pm$ 1.6	10.1 $\pm$ 1.3	-0.076	0.960
LVAWT (mm)	9.5 $\pm$ 1.2	9.5 $\pm$ 1.1	9.6 $\pm$ 1.2	-0.217	0.640
LVDD (mm)	48.4 $\pm$ 5.6	48.4 $\pm$ 5.3	48.6 $\pm$ 6.2	-0.727	0.786
LVSD (mm)	32.8 $\pm$ 6.4	32.5 $\pm$ 6.1	33.7 $\pm$ 7.2	-1.647	0.187
PAD (mm)	22.3 $\pm$ 2.5	22.4 $\pm$ 2.5	22.1 $\pm$ 2.4	0.590	0.362
RAD (mm)	37.5 $\pm$ 5.6	37.6 $\pm$ 5.9	37.3 $\pm$ 4.9	0.102	0.775

DC: Deceleration capacity; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVEF: Left ventricular ejection fraction; LVFS: Left ventricular shortening fraction; LAD: Left atrial diameter; AS: Aortic sinus; AVR: Aortic valve ring; AA: Ascending aorta; RVAW: Right ventricular anterior wall; IVS: Interventricular septal; LVAWT: Left ventricular anterior wall thickness; LVDD: Left ventricular end diastolic dimension; LVSD: Left ventricular end diastolic dimension; PAD: Pulmonary artery diameter; RAD: Right atrial diameter; SD: Standard deviation.

performed using IBM SPSS Version 23.0 (IBM Inc., Chicago, IL, USA). Two-sided *P* values less than 0.05 were considered statistically significant.

## Results

### Study patients

Medical records of 1390 patients with AF were originally collected during the study period. Of these patients, 196 patients were excluded due to the presence of valvular heart disease or prior cardiac valve surgery, 409 patients were excluded because of insufficient basic clinical data and Holter ECG recordings, and 526 patients were excluded because of all-day persistent AF or not sinus rhythm during Holter ECG recording. Finally, 259 patients with paroxysmal AF without valvular diseases were included in this study. Of the investigated patients, 143 (55.2%) were male. The mean patient age was 66.4  $\pm$  12.0 years (range, 24.0-90.0 years), and the mean BMI was 23.5  $\pm$  3.3 kg/m<sup>2</sup>. The mean DC value was 5.8  $\pm$  2.1 ms, with 27.4% of patients show abnormal DC values.

### Baseline clinical characteristics

The entire cohort was divided into two groups, according to their calculated DC values: 188 patients with DC values  $>$ 4.5 ms were assigned to the normal DC group and 71

patients with DC values  $\leq$ 4.5 ms were assigned to the abnormal DC group. No significant between-group differences were observed in sex, BMI, blood pressure on admission or smoking. Patients in the abnormal DC group were older than those in normal DC group (70.2  $\pm$  11.2 *vs.* 65.0  $\pm$  12.0 years, *P* = 0.002). The baseline characteristics are shown in Table 1. Additionally, no significant differences were identified in most of the echocardiography parameters. However, LVEF (61.3%  $\pm$  8.1% *vs.* 57.7%  $\pm$  10.5%, *P* = 0.014) and left ventricular fraction shortening (33.2%  $\pm$  5.5% *vs.* 30.8%  $\pm$  6.9%, *P* = 0.014) were observed larger in patients with normal DC group compared with low DC group.

### Concomitant diseases and drug therapies

As shown in Table 2, no significant between-group differences were identified in the prevalence of CAD (20.7% *vs.* 19.7%, *P* = 0.855), cardiomyopathy (3.2% *vs.* 2.8%, *P* = 0.876), diabetes (11.7% *vs.* 18.3%, *P* = 0.165), and hyperthyroidism (3.2% *vs.* 5.6%, *P* = 0.363). In contrast, patients in the abnormal DC value group had a higher prevalence of hypertension (48.4% *vs.* 62.0%, *P* = 0.024), heart failure (33.0% *vs.* 49.3%, *P* = 0.016), previous stroke/TIA (9.6% *vs.* 26.8%, *P* = 0.001) than those with normal DC values. There was no significant

**Table 2: Concomitant diseases and drug therapies in the general study population.**

Clinical parameters	All patients (n = 259)	Normal DC group (n = 188)	Abnormal DC group (n = 71)	$\chi^2$	P
Concomitant diseases					
Hypertension, n (%)	135 (53.7)	91 (48.4)	44 (62.0)	4.129	0.024
Diabetes, n (%)	35 (13.5)	22 (11.7)	13 (18.3)	5.687	0.165
Heart failure, n (%)	97 (37.5)	62 (33.0)	35 (49.3)	12.127	0.016
Previous Stroke/TIA, n (%)	37 (14.3)	18 (9.6)	19 (26.8)	17.203	0.001
CAD, n (%)	53 (20.5)	39 (20.7)	14 (19.7)	0.434	0.855
Cardiomyopathy, n (%)	8 (3.0)	6 (3.2)	2 (2.8)	0.090	0.876
Hyperthyroidism, n (%)	10 (3.9)	6 (3.2)	4 (5.6)	0.756	0.363
Drug therapies					
All drugs*, n (%)	211 (81.4)	148 (78.7)	63 (88.7)	1.573	0.286
$\beta$ -blockers, n (%)	155 (59.8)	106 (56.4)	49 (69.0)	2.240	0.159
ACEI, n (%)	65 (25.1)	43 (22.9)	22 (31.0)	1.374	0.266
ARB, n (%)	32 (12.4)	19 (10.1)	13 (18.3)	2.791	0.140
CCB, n (%)	65 (25.1)	47 (25.0)	18 (25.4)	0.010	1.000
Amiodarone, n (%)	56 (21.6)	42 (22.3)	14 (19.7)	0.358	0.617

\* Any one or more of the following five types of drugs are used. DC: Deceleration capacity; TIA: Transient ischemic attack; CAD: Coronary artery disease; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker.

**Table 3: Multivariable analysis of the risk factors associated with abnormal DC in patients with paroxysmal AF.**

Variables	P	OR	95% CI	B	Wald
Age	0.128	1.023	0.994–1.053	0.018	1.564
Heart failure	0.122	1.615	0.880–2.967	0.772	6.101
Hypertension	0.408	1.303	0.696–2.436	0.192	0.352
Previous stroke/TIA	0.006	2.861	1.356–6.039	1.338	11.722

DC: Deceleration capacity; AF: Atrial fibrillation; OR: Odds ratio; CI: Confidence interval; TIA: Transient ischemic attack.

difference in drug therapies between the two groups, whether single or multiple drugs were used, for specific statistics [Table 2].

In the multivariate analysis, we generated a statistical model that included the risk factors that were identified as being significantly associated with abnormal DC, including age, hypertension, heart failure, and previous stroke/TIA. After additionally adjusting for these factors above, patients with a history of previous stroke/TIA (odds ratio = 2.861, 95% confidence interval: 1.356–6.039,  $P = 0.006$ ) was independent associated with abnormal DC values in patients with paroxysmal AF [Table 3].

### Stroke risk scores

Full assessments of stroke risk were available for all 259 subjects. The mean CHADS<sub>2</sub> score of the included patients was  $1.63 \pm 1.43$ , and the mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was  $3.00 \pm 1.95$ . As shown in Table 4, the abnormal DC group had both higher CHADS<sub>2</sub> scores ( $2.25 \pm 1.48$  vs.  $1.40 \pm 1.34$ ,  $P = 0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ( $3.76 \pm 1.95$  vs.  $2.71 \pm 1.87$ ,  $P = 0.001$ ). After we performed a risk stratification, based on the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, there were still significant differences in stroke risk between the two groups ( $P = 0.001$  and  $P = 0.022$ , respectively). Spearman rank correlation test show a negative correlation between DC with CHADS<sub>2</sub> ( $r = -0.290$ ,

$P < 0.001$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ( $r = -0.263$ ,  $P < 0.001$ ) [Table 4; Figure 1 and Figure 2].

### Discussion

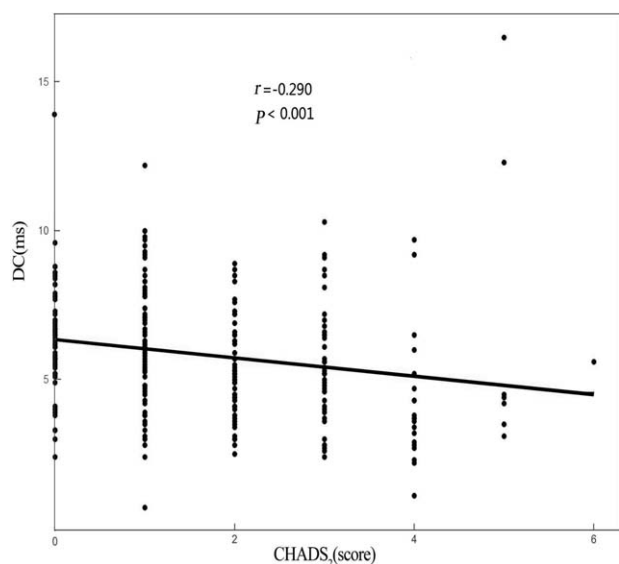
In this retrospective analysis of 259 patients with paroxysmal AF, the univariate analysis results showed that abnormal DC was associated with age, hypertension, heart failure, and previous stroke/TIA. After adjusting the above mixed factors, the further logistic regression analysis showed that previous stroke/TIA independently associated with DC values in patients with paroxysmal AF. The abnormal autonomic innervation plays an important role in cardiac modulation, meanwhile it is important in the mechanisms of AF. Recording of autonomic nerve activity can provide insight into its role in atrial arrhythmogenesis.<sup>[16]</sup> Abnormal DC are usually a manifestation of autonomic function imbalance. Although many researchers believe that the autonomic nervous function is abnormal in patients with AF, there is a need for exploring the influence factors on DC differences in patients with paroxysmal AF.

Many studies have shown that DC is decreased in patients with older age, hypertension, heart failure, or stroke,<sup>[17,18]</sup> which is consistent with our present results. DC was found significantly decreased after age 50, as the sympathetic tone pre-dominates and parasympathetic tone diminishes with age.<sup>[18]</sup> The average age of our research cohort is

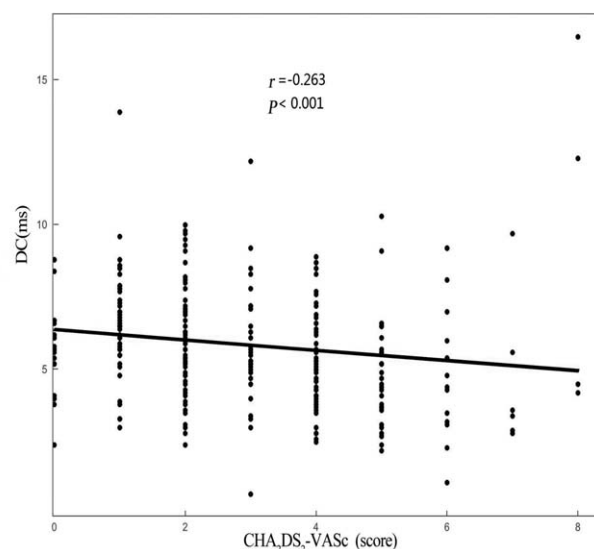
**Table 4: Between-group differences in CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.**

Scores	All patients (n = 259)	Normal DC group (n = 188)	Abnormal DC group (n = 71)	$\chi^2$	P
<b>CHADS<sub>2</sub> score</b>					
Mean ± SD	1.63 ± 1.43	1.40 ± 1.34	2.25 ± 1.48	-4.907	0.001
Low risk (Score = 0), n (%)	68 (26.3)	58 (30.9)	10 (14.1)	17.000	0.001
Medium risk (Score = 1), n (%)	70 (27.0)	56 (29.8)	14 (19.7)		
High risk (Score ≥2), n (%)	121 (46.7)	74 (39.4)	47 (66.2)		
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>					
Mean ± SD	3.00 ± 1.95	2.71 ± 1.87	3.76 ± 1.95	-4.847	0.001
Low risk (Score = 0), n (%)	22 (8.5)	17 (9.0)	5 (7.0)	7.664	0.022
Medium risk (Score = 1), n (%)	44 (17.0)	39 (20.7)	5 (7.0)		
High risk (Score ≥2), n (%)	193 (74.5)	132 (70.2)	61 (85.9)		

DC: Deceleration capacity; SD: Standard deviation.



**Figure 1:** Correlation between CHADS<sub>2</sub> scores and DC in 259 patients. DC: Deceleration capacity.



**Figure 2:** Correlation between CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and DC in 259 patients. DC: Deceleration capacity.

66.4 ± 12.0 years, which is older than 50 years. In addition, the proportion of patients older than 75 years is larger in abnormal DC group, DC values was significantly lower in this group, this also agreed with the current knowledge. Hypertension is known as an independent risk factor that can lead to electrical and structural alterations in the left atrium thereby predisposing to AF. It has been found positive associations between hypertension and CANS dysfunction.<sup>[19]</sup> DC abnormalities have certain predictive value for the prognosis of patients with chronic heart failure. When patients with AF combined with heart failure (HF), a synergistic effect of adrenergic nervous disorders might reduce sympathetic nervous distribution and enhance tone.<sup>[20]</sup> DC was also reported to had a dose-dependent relationship with HF exacerbation grade in patients with dilated cardiomyopathy.<sup>[21]</sup> In addition, although one of the most frequent manifestations of diabetic autonomic neuropathy is CANS affecting around 20% of patients with diabetes,<sup>[22]</sup> but there is no significant difference of complicated with diabetes between the two groups in our study. It can be inferred that the negative correlation between DC values and the above two stroke risk scores should related to other complications,

such as age, hypertension, heart failure, previous history of stroke/TIA. Previous studies have shown that several drugs, such as β-blockers, ACEI, ARB, CCB, might have great influence on cardiac autonomic function, but there were no significant differences in drug treatment between the two groups. This suggests that the decrease in DC in patients with paroxysmal AF in this study is not due to the use of the drugs above. Therefore, all these factors described above is closely associated with abnormal cardiac autonomic nervous function in paroxysmal AF.

Older age, hypertension, heart failure, and previous stroke/TIA have been established as independent risk factors for stroke or TE in the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc score systems in patients with AF. Therefore, we want to further see the correlation between the DC value and stroke risk assessment in paroxysmal AF. As a retrospective study, we performed the Spearman rank correlation tests to study the correlations between DC values and CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. It is interesting to note, our results firstly demonstrated prediction value of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were negatively associated with DC values in patients with paroxysmal AF. CHADS<sub>2</sub> and

CHA<sub>2</sub>DS<sub>2</sub>-VASc score systems are primarily used for stroke risk prediction in patients with AF, with advantages of practical and identifying low-risk patients, respectively. However, these systems only consider clinical factors, without considering the indexes that reflect other factors that have been verified as being related to stroke risks, such as kidney dysfunction and inflammatory response. Recently, a novel ABC scoring system has incorporated high-sensitivity cardiac troponin and N-terminal pro-brain natriuretic peptide, and it has been shown to have a better predictive effect for stroke risk.<sup>[23]</sup> Therefore, it is valuable to explore novel markers for stroke risk assessments and clinical decision making.

DC has been confirmed decreased in patients with hemispheric infarction, and correlated with the severity of stroke.<sup>[17]</sup> Cerebrovascular hemodynamics, which is called circulatory autoregulation are essential for the brain.<sup>[24]</sup> Slow blood pressure and flow changes are physiologically controlled by the sympathetic nervous system, therefore, it is possible that abnormal DC triggers changes in cerebral vascular pressure and flow.<sup>[25]</sup> In a rapid pacing AF model, atrial myocardium has significant and inhomogeneous neuronal eruption and sympathetic over-distribution.<sup>[26]</sup> Furthermore, increased CANS activity can lead to arterial stiffness and increase vascular resistance.<sup>[27]</sup> As a result, patients with AF are more likely to cause hemodynamic changes and cerebral infarction due to autonomic nervous function and distribution disorders. So cerebrovascular hemodynamics, CANS and AF are closely related. Our results show that lower DC is closely associated with stroke risk, and could be a potential indicator of stroke risk in patients with paroxysmal AF.

There are several limitations to this study. First, due to the retrospective study design, data were extracted from the medical record system at a single center. Some data were incomplete to preventing further subgroup analysis. In future, we can consider multi-center, prospective studies, and expand the sample size in order to obtain higher level evidence. Second, many medications act directly or indirectly on the autonomic nervous system. Although our study found no difference in drug treatment between the two groups, only the use of drugs during hospitalization was collected and may bias the results. Finally, the study subjects were limited to patients who were admitted to the cardiovascular department, which would lead to bias.

Abnormal DC is independently associated with previous stroke/TIA in patients with paroxysmal AF. DC values were correlated negatively with higher stroke risk scores in patients with paroxysmal AF. Further studies for the predictive value of DC for the stroke risk of paroxysmal AF are deserved.

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### Conflicts of interest

None.

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