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Deep terminal negativity of the P-wave in V1 and stroke risk: The National Health and Nutrition Examination survey III

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Abstract

Background: Deep terminal negativity of the P-wave in V1 (DTNPV1) was considered if the absolute value of the depth of the negative phase was >100 μV in the presence of a biphasic P-wave in V1. In this study, we aimed to determine the association between DTNPV1, a simpler P-wave index, and the risk of stroke.

Methods: We compared P-wave indices between participants with and without a self-reported history of stroke in the United States Third National Health and Nutrition Examination Survey (NHANES III). The association between DTNPV1 and stroke was quantified with logistic regression models.

Results: In total, 7732 participants were included (307 with a history of stroke). Patients with stroke had deeper terminal negativity of the P-wave in V1 (52.3 ± 33.9 μV vs. 41.4 ± 27.0 μV, $p < .001$). After adjustment, DTNPV1 was associated with an increased risk of stroke (OR: 1.63, 95% CI: 1.03–2.60, $p = .038$). This association appeared to be stronger in people aged <75 years (interaction $p = .023$), and in those without heart failure (interaction $p = .018$) or ischemic heart disease (interaction $p = .014$). In contrast to the participants with 0 or ≥2 risk factors, in those with 1 risk factor, stroke prevalence was significantly different among the three categories of terminal negativity of the P-wave (0 μV, >0 μV but ≤100 μV and > 100 μV) in V1 (2.8%, 3.3%, and 10.3%, respectively, $p = .005$).

Conclusion: In NHANES III, DTNPV1 was associated with a higher prevalence of stroke, suggesting that DTNPV1 might be a convenient marker to distinguish the risk of stroke.

KEYWORDS
electrocardiogram, P-wave indices, risk of stroke

1 | INTRODUCTION

Atrial fibrillation (AF) is related to a 4–5-fold increased risk of stroke. (Wolf et al., 1991) In AF patients, the CHA_2DS_2-VASc score is recommended as the principal risk-stratification scheme for stroke and thromboembolism, helping doctors make clinical decisions for anticoagulation in everyday practice. (Hindricks et al., 2020) However, the properties of AF, such as the type of AF and AF burden, are not included in this scheme. In the meantime, all the components in the CHA_2DS_2-VASc score are known to cause atrial cardiomyopathy. It

has been recently proposed that the presence of AF might not be a prerequisite for left atrial thrombogenesis, and atrial cardiomyopathy might contribute to thrombogenesis independent of AF.(Bisbal et al., 2020; Sajeev et al., 2020; Shen et al., 2019) This notion was further supported by observations from some studies indicating a temporal disassociation between subclinical AF and stroke in patients with implantable devices. (Martin et al., 2015; Brambatti et al., 2014; Daoud et al., 2011)

P-wave indices (PWIs) are electrocardiographic (ECG) markers of atrial activation. Abnormal PWIs reflect underlying atrial remodeling. (Ariyarajah et al., 2005; Goyal & Spodick, 2001; Nakatani et al., 2020) P-wave terminal forces in V1 (PTFV1) have long been considered a measure of left atrial activation and interatrial conduction. An abnormal PTFV1 has been shown to be associated with AF occurrence (Huang et al., 2020), ischemic stroke (Okin et al., 2016; Yaghi et al., 2016; Kamel et al., 2015a), left ventricular hypertrophy (Romhilt & Estes Jr., 1968), heart failure, and mortality. (Liu et al., 2013) However, the determination of PTFV1 requires measurements of both the depth and duration of the downward terminal deflection P-wave in V1, which might be time-consuming in daily practice. Observational results from the Atherosclerosis Risk In Communities (ARIC) study showed that the terminal negativity of the P-wave in V1 > 100 μV is always accompanied by a duration >40 ms. (Tereshchenko et al., 2014) Thus, we hypothesized that deep terminal negativity of the P-wave in V1 (DTNPV1), a simplified P-wave index, might be associated with the risk of stroke.

2 | METHODS

2.1 | Study population

The National Health and Nutrition Examination Survey (NHANES) is a nationwide survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. The NHANES aims to assess the health and nutritional status of adults and children in the United States of America. The design of the NHANES was previously published. (National Center for Health Statistics, 1994) The NHANES database includes demographic information, health-related questions, physiological measurements, and laboratory tests. The third National Health and Nutrition Examination Survey (NHANES III) was conducted from 1988 to 1994.

2.2 | Definition of prevalent hypertension, diabetes, hypercholesterolemia, and stroke

Hypertension was defined as a self-reported history, the use of antihypertensive medications or a systolic blood pressure > 140 mmHg and/or a diastolic blood pressure > 90 mmHg at the time of the interview. Body mass index was calculated using weight and standing height in the survey. Subjects were considered to have diabetes mellitus if they reported a history or had a serum glucose level ≥ 126 mg/dL after fasting for longer than 8 h. Hypercholesterolemia was defined as a self-reported history or a total cholesterol level ≥ 240 mg/dL. Stroke outcome was examined using the question "Has a doctor ever told you that you had a stroke?"

2.3 | ECG recordings and measurements of the amplitude of the terminal negative phase of the P-wave in V1

In NHANES III, 8561 participants underwent a standard 12-lead ECG at rest using the Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, WI, USA). The evaluation standards of the ECG quality were posted on the NHANES website. (NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY III, 1991) ECG parameters were automatically measured at the EPICARE Center at the Wake Forest School of Medicine, Winston Salem, NC. Major or minor ECG abnormalities were examined according to the Minnesota and Novacode algorithms. We considered the existence of DTNPV1 if the absolute value of the depth of the negative phase was >100 μV in the presence of a biphasic P-wave in V1. Figure 1 shows the measurement of the amplitude of the terminal negative phase of the P-wave in V1. In our study, 74 with unmeasurable sinus P-waves due to pacemakers and arrhythmia were excluded. After further exclusion

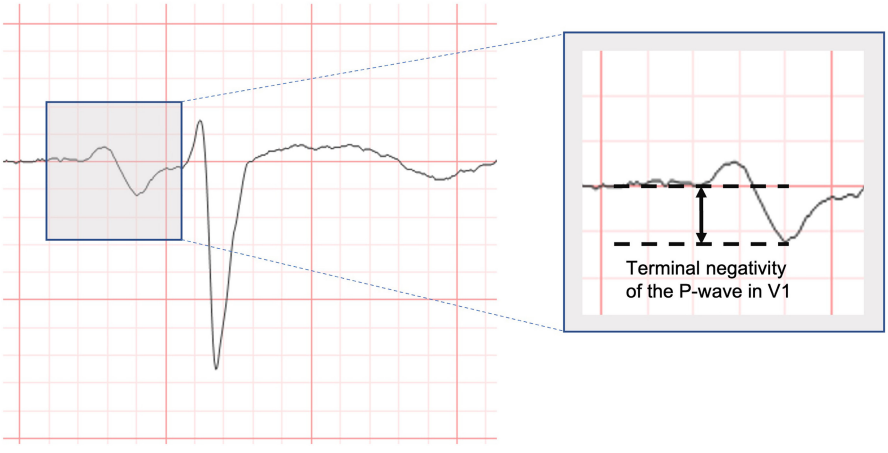

FIGURE 1 Measurement of terminal negativity of the P-wave in V1

of participants with missing data, 7732 individuals were included in our analysis.

2.4 | Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Differences between the patients with and without stroke were tested using an unpaired Student's *t*-test if normally distributed or the Mann-Whitney *U* test if non-normally distributed. Categorical variables are presented as counts with percentages and were compared using the chi-squared test or Fisher's exact test for low expected counts ($n < 5$).

The association between the amplitude of the terminal negative phase of the P-wave in V1 and stroke was modeled with an unadjusted restricted cubic spline. Logistic regression models were used to quantify the association between DTNPV1 and stroke. For the stroke endpoint, we constructed 4 models: Model 0 was an adjusted model. Model 1 included the following demographic variables: age, race, and sex. Model 2 included prevalent cardiovascular diseases (ischemic heart disease, heart failure), risk factors (diabetes, smoking, drinking, hypercholesterolemia, hypertension, body mass index, serum creatinine level) and major noncardiovascular comorbidities (thyroid disease and cancer) in addition to demographics. Model 3 was further adjusted for electrocardiographic abnormalities (major and minor ECG abnormalities as detected by the Minnesota code). The interaction between DTNPV1 and the other variables was tested in the subgroup analyses, including age (using 75 years as a cutoff value), race, sex, heart failure, hypertension, hypercholesterolemia, diabetes mellitus, ischemic heart disease, cancer, and thyroid disease. Moreover, we calculated each individual's number of risk factors for cardiovascular disease (CVD) in the components of the $CHADS_2$ score (except for stroke), including congestive heart failure, hypertension, age > 75 years, and diabetes mellitus. The prevalence of stroke was stratified by the combination of the number of risk factors and the category of terminal negativity of the P-wave in V1 (absolute amplitude of the negative phase of terminal negativity of the P-wave in V1 of 0 μV, >0 μV but ≤100 μV and > 100 μV). All analyses were performed using SPSS (IBM). A $p < .05$ was considered statistically significant.

3 | RESULTS

In total, 7732 participants with adequate information were included. The mean age was 59.9 ± 13.4 years, with 48.1% of the sample being male. In the entire study, 307 patients had a self-reported history of stroke. The demographic, clinical, laboratory, and electrocardiographic characteristics of the participants with and without stroke are compared in Table 1. In addition to being older and more likely to have cardiovascular comorbidities, patients with stroke had a greater P-wave axis degree (61.9 ± 22.8° vs. 58.5 ± 22.6°, $p = .011$), a higher heart rate (70.1 ± 12.8 bpm vs. 68.4 ± 11.4 bpm, $p = .025$), a longer P-wave duration (115.7 ± 20.9 ms vs. 112.2 ± 15.1 ms, $p = .004$), a longer PR interval (172.1 ± 31.6 ms vs. 164.3 ± 28.4 ms, $p < .001$), smaller positivity of the P-wave in V1 (43.4 ± 28.6 μV vs. 48.2 ± 28.7 μV, $p = .004$) and deeper terminal negativity of the P-wave in V1 (52.3 ± 33.9 μV vs. 41.4 ± 27.0 μV, $p < .001$) than the participants without stroke. DTNPV1 was observed in 232 individuals (3.0%) in this study (24 with stroke and 208 without stroke). In addition, major (33.6% vs. 16.6%, $p < .001$) and minor (25.7% vs. 21.5%, $p < .001$) ECG abnormalities were more common in participants with stroke than those without stroke.

Figure 2 depicts that the prevalence of stroke increased curvilinearly with the deeper terminal negativity of the P-wave in V1, modeled using an unadjusted restricted cubic spline. The prevalence rate of stroke was 10.3% in the participants with DTNPV1 and 4.0% in those without DTNV1. After adjusting for demographic characteristics (age, sex, and race), clinical characteristics, including prevalent cardiovascular diseases (ischemic heart disease and heart failure), risk factors (diabetes, smoking, drinking, hypercholesterolemia, hypertension, body mass index, and serum creatinine level), major noncardiovascular comorbidities (thyroid disease and cancer) and electrocardiographic abnormalities (major and minor ECG abnormalities as detected by the Minnesota code), the association between DTNPV1 and the risk of stroke was not attenuated (OR: 1.63, 95% CI [1.03–2.60], $p = .038$), as shown in Table 2.

Then, we examined the association in multiple subgroups. Although the association between DTNPV1 and stroke was consistent across the majority of the subgroups, it appeared to be stronger in people aged <75 years (interaction $p = .023$) and in those without heart failure (interaction $p = .018$) or ischemic heart disease (interaction $p = .014$), as shown in Figure 3.

Table 3 shows the prevalence of stroke grouped by the number of risk factors and the categories of terminal negativity of the P-wave in V1. In the group of participants with 0 or ≥2 risk factors, the prevalence of stroke did not differ among the three groups when categorized based on the absolute amplitude of the negative phase of the P-wave in V1. In the participants with a single risk factor, the prevalence of stroke was 2.8%, 3.3%, and 10.3% in the three groups of P-wave negativity in V1 (0 μV, >0 μV but ≤100 μV and > 100 μV), respectively, with a statistically significant difference ($p = .005$).

4 | DISCUSSION

In this large cross-sectional analysis of the NHANES III, ECG signs of DTNPV1 were associated with a higher prevalence of stroke, independent of CVD risk factors. This association appeared to be stronger in people aged <75 years, in those without heart failure or ischemic heart disease, and in those at intermediate risk for cardiovascular diseases. Our findings suggest that DTNPV1 might be an intermediate marker in the pathway linking atrial cardiomyopathy and stroke.

TABLE 1 Comparisons of demographic, clinical, laboratory, and electrocardiographic characteristics of patients with and without stroke

	Stroke ($n = 307$)	No stroke ($n = 7425$)	p value
Demographics			
Age at interview (years)	70.3 ± 11.4	59.4 ± 13.3	<.001
Men	162 (52.8%)	3558 (47.9%)	.096
White	224 (73.0%)	5496 (74.0%)	.679
Clinical characteristics			
$CHADS_2$ score	3.5 ± 0.8	0.8 ± 0.8	<.001
Heart failure	51 (16.6%)	319 (4.3%)	<.001
Hypertension	234 (76.2%)	3670 (49.4%)	<.001
Hypercholesterolemia	148 (48.2%)	3031 (40.8%)	.010
Diabetes mellitus	61 (19.9%)	833 (11.2%)	<.001
Ischemic heart disease	82 (26.7%)	434 (5.8%)	<.001
Thyroid disease	18 (5.9%)	394 (5.3%)	.670
Cancer	60 (19.5%)	788 (10.6%)	<.001
Current smoker	62 (20.2%)	1677 (22.6%)	.326
Current drinker	19 (6.2%)	1378 (18.6%)	<.001
Body mass index (kg/m^2)	27.6 ± 5.8	27.7 ± 5.5	.809
Systolic blood pressure (mmHg)	143.7 ± 19.8	132.6 ± 19.8	<.001
Diastolic blood pressure (mmHg)	76.1 ± 11.0	76.3 ± 10.3	.749
Laboratory results			
Total cholesterol concentration (mg/dL)	224.7 ± 49.6	217.9 ± 43.8	.019
Total triglyceride concentration (mg/dL)	182.8 ± 128.5	162.9 ± 132.0	.010
Creatinine concentration (mg/dL)	146.0 ± 1126.7	136.4 ± 1088.0	.879
Serum glucose (mg/dL)	118.2 ± 52.6	108.7 ± 44.1	.002
Electrocardiographic characteristics			
Heart rate (bpm)	70.1 ± 12.8	68.4 ± 11.4	.025
P-wave axis (°)	61.9 ± 22.8	58.5 ± 22.6	.011
P-wave duration (ms)	115.7 ± 20.9	112.2 ± 15.1	.004
P-wave amplitude positive, II (μV)	132.6 ± 52.7	133.9 ± 47.4	.687
P-wave amplitude positive, V1 (μV)	43.4 ± 28.6	48.2 ± 28.7	.004
P-wave terminal negativity, V1 (μV)	−52.3 ± 33.9	−41.4 ± 27.0	<.001
DTNPV1 (%)	24 (7.8%)	208 (2.8%)	<.001
PR interval (ms)	172.1 ± 31.6	164.3 ± 28.4	<.001
Major ECG abnormalities	103 (33.6%)	1231 (16.6%)	<.001
Minor ECG abnormalities	79 (25.7%)	1597 (21.5%)	.048

Continuous variables are expressed as the mean ± SD. Categorical variables are presented as numbers (percentages).

Abbreviations: bpm, beats per minute; DTNPV1, terminal negativity of the P-wave in V1; ECG, electrocardiogram.

In the normal population, the P-wave in lead V1 is always biphasic-positive in the initial phase and negative in the terminal phase. Atrial activation starts in the right atrium, and the P-wave vector points forward, which displays a positive deflection in V1. The sequentially activated left atrium turns the P-wave vector away from V1 and, therefore, displays a negative deflection. The absolute

negative amplitude of the P-wave in lead V1 is normally <100 μV. The product of the amplitude and duration of the P-wave negative deflection is defined as PTFV1. The metric was initially used for the diagnosis of valvular heart disease. (Morris Jr. et al., 1964)

Emerging studies have proven an association between abnormal P-wave indices and increased stroke risk in the setting without AF. (Kamel et al., 2015a; Kamel et al., 2015b; Kamel et al., 2014) Hence, the concept of atrial cardiomyopathy is proposed to be a critical contributor to thrombogenesis in the atrium. Atrial cardiomyopathy was deemed the substrate for atrial electrical remodeling, structural remodeling, endothelial dysfunction, and the hypercoagulable state. (Goette et al., 2016) Although there are no definite criteria for diagnosing atrial cardiomyopathy, the P-wave indices can reflect atrial electrical remodeling to some extent. (Janin et al., 2010) The association between abnormal P-wave indices and atrial structural remodeling has been well established in previous reports in a group of patients with structural heart disease without AF. DTNPV1 showed a stronger correlation with the left atrial volume index and global left atrium emptying fraction measured by cardiac magnetic resonance than other P-wave indices, including the P-prime duration in V1, PTFV1, P-wave duration, and P-wave axis. (Tiffany Win et al., 2015)

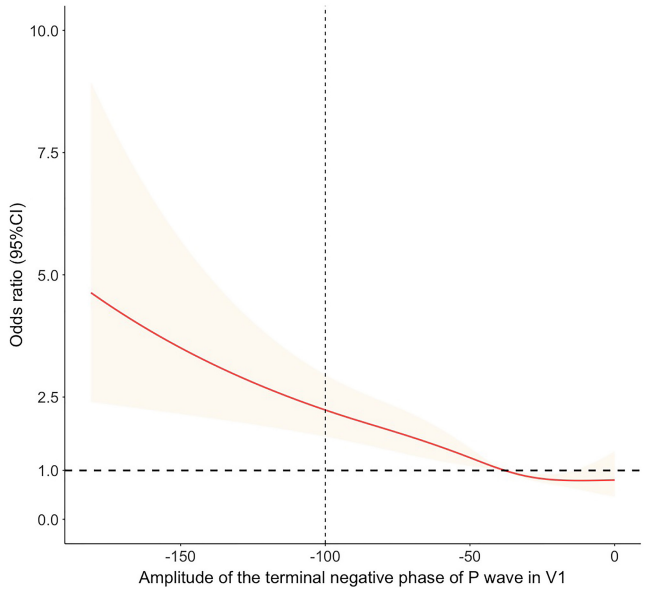

FIGURE 2 The relationship between the prevalence of stroke and the amplitude of the terminal negative phase of the P-wave in V1 modeled using an unadjusted restricted cubic spline. Data are presented with odds ratios (ORs, solid red line) and 95% confidence intervals (gray areas)

The association of DTNPV1 and stroke found in our study indicates that DTNPV1 is an ECG marker that is associated with the risk of stroke through an embolic mechanism. However, due to the absence of the classification of stroke etiology in the NHANES III database, we could not further examine the association between DTNPV1 and different types of stroke. The interaction analysis in the subgroups may be considered hypothesis-generating. Old age, heart failure, and ischemic heart disease all indicate a heavier cardiovascular burden. The stronger association between DTNPV1 and stroke in younger participants without ischemic heart disease and heart failure suggests that DTNPV1 may be of greater clinical significance in relatively healthy patients. Moreover, we also found that the association between stroke and DTNPV1 was stronger in participants at intermediate risk of CVD (with 1 risk factor) than in those at low (without any risk factors) or higher risk (with 2–4 risk factors). Our findings were in line with the results from previous studies. In a case-control study that focused on young ischemic stroke patients with few comorbidities, PTFV1 was found to be associated with the cardioembolic subtype rather than the atherosclerotic subtype. (Pirinen et al., 2017) However, DTNPV1 is a more simplified index to measure than PTFV1 in our clinical practice. Taken together, our observations should encourage clinicians to suspect cardioembolic origin of the stroke in patients with intermediate CVD risk and DTNPV1.

5 | LIMITATIONS

Our study has some limitations. Due to its cross-sectional nature, the temporal and causal relationship between DTNPV1 and the risk of stroke could not be examined. Although potential confounders were adjusted in our study, we cannot exclude all residual confounders,

TABLE 2 Univariate and multivariable logistic regression analysis to show the association between deep terminal negativity of the P-wave in V1 and stroke

	OR	95% CIs	*p*
Model 0. Unadjusted	2.94	1.90–4.56	<.001
Model 1. Adjusted for demographics	2.18	1.39–3.41	.001
Model 2. Adjusted for demographics and clinical characteristics	1.69	1.06–2.68	.026
Model 3. Adjusted for demographics, clinical characteristics and ECG abnormalities	1.63	1.03–2.60	.038

Demographic characteristics included age, sex, and race; clinical characteristics included prevalent cardiovascular diseases (ischemic heart disease, heart failure), risk factors (diabetes mellitus, smoking, drinking, hypercholesterolemia, hypertension, body mass index, serum creatinine level), major noncardiovascular comorbidities (thyroid disease and cancer); and ECG abnormalities included major and minor ECG abnormalities as detected by the Minnesota code.

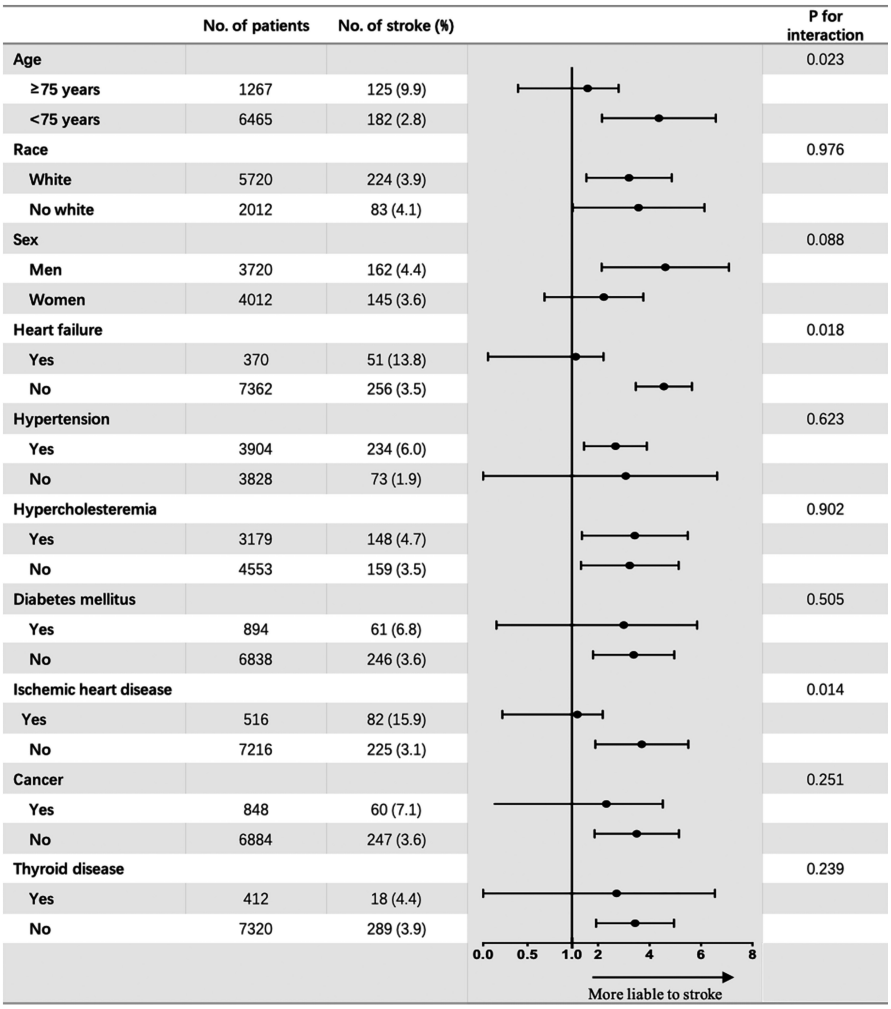

FIGURE 3 Deep terminal negativity of the P-wave in V1 and the risk of stroke across the subgroups

TABLE 3 The prevalence of stroke grouped by the number of risk factors and terminal negativity of the P-wave in V1

		Risk factors			
n = 7732		None *n* = 3143 (40.7%)	1 *n* = 2977 (38.5%)*	2 *n* = 1392 (18.0%)	3 or 4 *n* = 220 (2.8%)
Absolute amplitude of the negative phase of the P-wave in V1	0 μV *n* = 236 (3.0%)	1/125 (0.8%)	2/71 (2.8%)	5/32 (15.6%)	1/8 (12.5%)
	>0 μV but ≤100 μV *n* = 7264 (94.0%)	33/2972 (1.1%)	94/2809 (3.3%)	117/1286 (9.1%)	30/197 (15.2%)
	>100 μV *n* = 232 (3.0%)	1/46 (2.2%)	10/97 (10.3%)	12/74 (16.2%)	1/15 (6.7%)

Risk factors included congestive heart failure, hypertension, an age > 75 years, and diabetes mellitus.

*The difference in the prevalence of stroke was statistically significant ($p < .05$).

including unmeasured factors and unknown factors. Second, the ECG parameters in the NHANES III database were measured automatically by analytical software. Thus, whether abnormal terminal negativity of the P-wave in V1 estimated by the naked eye could be of the same clinical value remains unknown. Third, more comprehensive assessments of the P-wave indices, history of AF, and detailed stroke subtypes were unavailable in the NHANES III database. Therefore, we are not able to further analyze DTNPV1 in specific subgroups of patients, particularly, in patients with a history of paroxysmal AF or with cardioembolic stroke. Nevertheless, our findings contribute to emerging evidence that atrial cardiomyopathy marked by ECG parameters may be associated with stroke risk.

6 | CONCLUSION

In a large population of adults in the United States, DTNPV1 was associated with a higher prevalence of stroke, especially in people

aged <75 years, and in those without heart failure or ischemic heart disease. The association between DTNPV1 and stroke was stronger in people at intermediate risk for CVD than in those at low or high risk. DTNPV1 is likely to reflect underlying atrial cardiomyopathy and merits further study to elucidate its relationship with the risk of stroke.

AUTHOR CONTRIBUTIONS

The review concept and design were developed jointly by all authors. All authors contributed to the design, the data interpretation, and all provided input in each draft of the manuscript.

CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

The NHANES III protocol was approved by the Research Ethics Review Board of the National Center for Health Statistics. Informed consent was obtained from each participant.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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