Global cognitive function correlates with P-wave dispersion in frail hypertensive older adults

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Abstract
P-Wave Dispersion (PWD) is an ECG parameter defined as the difference between the longest and the shortest P-Wave duration. PWD has been associated with hypertension, a leading cause of age-related cognitive decline. Moreover, hypertension is associated with vascular dementia and Alzheimer’s Disease. Based on these considerations, we evaluated PWD and global cognitive function in frail hypertensive older adults with a previous diagnosis of cognitive decline. We evaluated consecutive frail hypertensive patients ≥65-year-old with a Mini-Mental State Examination (MMSE) score <26. Patients with evidence of secondary hypertension, history of stroke, myocardial infarction, or therapy with beta-blockers or acetylcholinesterase inhibitors were excluded. Beta-blocker therapy causes a significant decrease in PWD; patients treated with acetylcholinesterase inhibitors were not included to avoid confounding effects on cognitive function. By examining 180 patients, we found that PWD significantly correlated with MMSE score. Strikingly, these effects were confirmed in a linear multivariate analysis with a regression model. To our knowledge, this is the first study showing that PWD correlates with global cognitive function in frail hypertensive older adults.

KEYWORDS
cognitive function, ECG, frailty, hypertension, older adults

1 | BACKGROUND

P-Wave Dispersion (PWD) is a non-invasive parameter defined as the difference between the longest and the shortest P-Wave duration on the surface electrocardiogram (ECG), which has been investigated in atrial fibrillation (AF), hypertension, and stroke.

Frailty is a worldwide increasing health problem in the elders and a biological syndrome of decreased physiological reserves with increased vulnerability to stressors. Cognitive decline is one of the most serious social and economic problems. Careful prevention seems to be the best way to reduce the incidence of dementia, identifying risk factors of dementia and mild cognitive impairment (MCI). Cardiovascular diseases and their risk factors have been shown to have a strong impact on dementia and/or MCI, also because the brain is very sensitive to hemodynamic alterations. Hypertension is one of the most common diseases and its prevalence increases...
with age. Furthermore, it is a leading cause of age-related cognitive decline and is associated with vascular dementia and Alzheimer’s disease. Indeed, hypertension leads to chronic endothelial dysfunction contributing to atherosclerosis, inflammation, and oxidative stress.

However, no study exploring the correlation between PWD and cognitive impairment in frail hypertensive older adults is currently available. Based on these considerations, we sought to evaluate PWD and global cognitive function in frail hypertensive older adults with cognitive impairment.

2 METHODS

From March 2021 to September 2021, we evaluated 239 consecutive frail hypertensive older adults at the Local Health Authority (ASL) of Avellino and Naples ≥ 65-year-old with a Mini-Mental State Examination (MMSE) score < 26.

Patients with evidence of secondary hypertension, history of stroke, myocardial infarction, AF, or therapy with beta-blockers or acetylcholinesterase inhibitors were excluded. Indeed, beta-blocker therapy has been shown to cause a significant decrease in PWD; patients treated with acetylcholinesterase inhibitors were not included to avoid confounding effects on cognitive function. PWD was assessed via a digital computerized system, confirmed by manual measurements on paper.

An informed consent was signed by each patient (or legal representative). Research has been performed according to the 1975 Declaration of Helsinki and its later amendments. The Campania Nord Institutional Review Board approved the protocol.

2.1 Frailty assessment

Physical frailty assessment was performed following the Fried criteria; a diagnosis of frailty status was made with at least three points out of the following five:

- Weight loss (unintentional loss ≥ 4.5 kg in the past year);
- Weakness (handgrip strength in the lowest 20% quintile at baseline, adjusted for sex and body mass index);
- Exhaustion (poor endurance and energy, self-reported);
- Slowness (walking speed under the lowest quintile adjusted for sex and height);
- Low physical activity level (lowest quintile of kilocalories of physical activity during the past week).

2.2 Cognitive evaluation

Global cognitive function was assessed via the MMSE corrected for age and educational level of patients. This cognitive test covers many cognitive skills, and scores range from 0 to 30. MMSE is one of the most common and useful tests to evaluate global cognition and its score is influenced by demographic variables such as age and years of education. Cognitive impairment was defined by a MMSE Score < 26, as previously reported.

2.3 Statistical analysis

All data are shown as mean ± SD. We calculated the number of patients required for the study to reject the null hypothesis 95% of the time (i.e., with a one-tailed type II error rate of .05) with a two-tailed type I error at the .05 level of significance.

The sample size was calculated by G-POWER software. A linear multivariate analysis was performed with a regression model including age, blood pressure, heart rate, diabetes, dyslipidemia, and smoking status. A p < .05 was considered statistically significant. All calculations were performed using the software SPSS 26.

3 RESULTS

One eighty patients entered the database (Figure 1). The study group had a mean of 74.9 ± 5.4 years. A slightly higher number of patients were women, with modest overweight. All patients were previously diagnosed with hypertension and, according to age, most of them were affected by comorbidity (no one had a history of previous acute myocardial infarction, heart failure, or stroke). All patients were treated with oral antihypertensive agents (Table 1).

We observed that PWD significantly correlated with MMSE ($r^2$: .390; p < .001, Figure 2). The independent effects on MMSE score were tested in a linear multivariate analysis with a regression model.
TABLE 1  Clinical characteristics of our population

| Characteristic                  | Value                          |
|--------------------------------|--------------------------------|
| Number of patients             | 180                            |
| Age (years)                    | 74.9 ± 5.4 (66–90)             |
| Sex (M/F)                      | 82/98                          |
| BMI (kg/m²)                    | 28.1 ± 2.9 (25–36)             |
| SBP (mmHg)                     | 132.5 ± 10.3 (100–150)         |
| DBP (mmHg)                     | 81.6 ± 9.5 (50–90)             |
| HR (bpm)                       | 66.1 ± 8.7 (57–120)            |
| PWD (sec)                      | .06 ± .02 (0.03–0.08)          |
| Comorbidities                  |                                |
| Diabetes, n (%)                | 74 (41.1)                      |
| Dyslipidemia, n (%)            | 131 (72.8)                     |
| Smoking, n (%)                 | 73 (40.6)                      |
| Active treatments              |                                |
| ACE inhibitors, n (%)          | 106 (58.9)                     |
| Angiotensin receptor blockers, n (%) | 74 (41.1)                 |
| Calcium inhibitor, n (%)       | 65 (36.1)                      |
| Statins, n (%)                 | 128 (71.3)                     |
| Diuretic, n (%)                | 48 (26.7)                      |
| Aspirin, n (%)                 | 67 (37.6)                      |
| Clopidogrel, n (%)             | 24 (13.3)                      |
| Oral antidiabetic drugs, n (%) | 45 (25.0)                      |
| Insulin, n (%)                 | 29 (16.0)                      |
| Laboratory analyses            |                                |
| Fasting plasma glucose (mg/dl) | 119.2 ± 19.5 (84–191)          |
| Creatinine (mg/dl)             | .9 ± 2.7 (.7–1.4)              |
| Total cholesterol (mg/dl)      | 176.7 ± 32.7 (113–254)         |
| HDL cholesterol (mg/dl)        | 52.1 ± 16.2 (31–84)            |
| LDL cholesterol (mg/dl)        | 121.3 ± 23.3 (91–168)          |
| Global cognitive function      |                                |
| MMSE (range: 0–30)            | 19.1 ± 3.4 (11–25)             |

Note: Data are means ± SD (minimum, maximum values) for continuous variables or n (%) for categorical variables.
Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL: high-density lipoprotein; HR, heart rate; LDL: low-density lipoprotein; MMSE: Mini-Mental State Examination; PWD: P-wave dispersion.

(0.03–0.08), in which we found a significant effect of age (p < .001) and systolic blood pressure (p: .031).

4  | DISCUSSION

To the best of our knowledge, this is the first study demonstrating a significant relationship between PWD and global cognitive function in frail hypertensive older adults.

Frailty leads to a high risk of death and adverse outcomes in cardiovascular diseases.42–44

A previous report demonstrated that QRS duration was significantly associated to frailty in chronic hemodialysis patients and frailty contributed to the observed cardiovascular risk in end-stage renal disease.45 Similarly, another study evidenced that ECG abnormalities can predict a higher risk for later support/care-need certification in community-dwelling older adults with no prior history of cardiovascular disease.46

Our findings indicate that posing particular attention to a simple ECG parameter may help prevent or delay cognitive impairment, selecting patients to be screened via neuro-psychological tests or brain imaging, and identifying patients to be treated by pharmacological approaches. We confirmed our results with a linear regression multivariate analysis, showing the significant impact of age and systolic blood pressure; this result is very important in frailty because these subjects suffer from many diseases and a number of complications. Hence, a timely diagnosis of cognitive impairment should be very helpful to reduce the incidence of adverse outcomes and functional decline.

Furthermore, frail older adults with a diagnosis of hypertension should be carefully screened with ECG, echocardiography, 24- or 48-h ECG Holter, stress tests, and 24-h blood ambulatory blood pressure monitoring.47,48 We speculate that this kind of approach would bring to an early diagnosis and to a prompt therapeutic approach that could counteract cognitive dysfunction and/or delay the onset of cognitive impairment and dementia.

The exact mechanisms linking PWD and hypertension need to be investigated. Indeed, hypertension is known to lead to endothelial alterations and microvascular dysfunction, increasing inflammation and oxidative stress,49–58 which may underlie structural and electromechanical alterations in the heart.

Our study is not exempt from limitations. PWD can be influenced by a wide range of parameters, not only cardiovascular (for instance atrial size), but also endocrine, renal, and respiratory conditions59,60; unfortunately, we did not have these pieces of information available for all patients; additionally, we did not adjust our data by the severity of hypertension, the degree of left ventricular hypertrophy, or the control of diabetes. Evidently, our findings cannot be extended to younger pop-
TABLE 2  Linear multivariate analysis, performed with MMSE as dependent variable

|                | B   | Standard error | Beta | t    | p     | 95.0% CI Lower bound | 95.0% CI Upper bound |
|----------------|-----|----------------|------|------|-------|----------------------|---------------------|
| Age            | −.331 | .033       | −.619 | −9.988 | <.001 | −.396                | −.265                |
| SBP            | .071 | .033       | .223  | 2.170 | .031  | .006                | .136                |
| DBP            | −.065 | .041       | −.179 | −1.603 | .111  | −.145                | .015                |
| HR             | .034 | .030       | .081  | 1.126 | .262  | −.026                | .094                |
| Diabetes       | .033 | .428       | .005  | .076  | .939  | −.812                | .877                |
| Dyslipidemia   | −.179 | .526       | −.023 | −.339 | .735  | −1.218               | .861                |
| Smoking        | .618 | .467       | .088  | 1.322 | .188  | −.305                | 1.540                |

5 | CONCLUSION

Taken together, our data indicate that PWD on the ECG correlates with global cognitive function in frail hypertensive older patients. The results of our study are significant because they have evidenced a strong association between MMSE and PWD in the above-mentioned group.

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DISCLOSURE STATEMENT

The authors have nothing to disclose.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Coordination of the study was performed by Pasquale Mone and Gaetano Santulli. Data collection and analysis were performed by Pasquale Mone, Antonella Pansini, Stefano De Gennaro, Mafalda Esposito, Paolo Rinaldi, Antonio Colin, Fabio Minicucci, Antonio Coppola, and Salvatore Frullone. Statistical analysis was performed by Pasquale Mone, Francesco Calabrò, and Gaetano Santulli. Data interpretation was performed by all authors. Pasquale Mone and Gaetano Santulli prepared the manuscript. All authors reviewed and approved the final draft.

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