

How to Identify Patients at Risk of Silent Atrial Fibrillation after Cryptogenic Stroke: Potential Role of P Wave Dispersion

Maurizio Acampa,^a Pietro Enea Lazzerini,^b Giuseppe Martini^a

^aDepartment of Neurological and Sensorineural Sciences, General Hospital "Santa Maria alle Scotte", Azienda Ospedaliera Universitaria Senese, Siena, Italy

^bDepartment of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy

Dear Sir:

We have read with interest the article by Bridge and Thijs¹ focused on how selecting cryptogenic stroke patients to screen for atrial fibrillation (AF).

Cryptogenic stroke is an exclusion diagnosis, which is reached by ruling out known causes;² however, it is possible that a silent AF may play a key role in the pathogenesis of this kind of stroke.³ In recent years, the use of prolonged outpatient cardiac monitoring has led to detection of low-burden AF in 15% of cryptogenic stroke patients.²

Bridge and Thijs emphasize resting electrocardiographic findings as simple and effective markers for selecting patients who should undergo further electrocardiogram (ECG) monitoring.¹ Since it is really difficult and expensive to perform prolonged ECG monitoring in all cryptogenic strokes, resting 12-lead ECG parameters could help to identify subgroups of patients to submit to further ECG monitoring.⁴

Nevertheless, Bridge doesn't take account of P wave dispersion (PWD), a well-known ECG parameter, predictor of AF.⁵ PWD is defined as the difference between the maximum and the minimum P wave duration detected in a 12-lead ECG. A standard 12-lead ECG is generally used to measure PWD: P wave duration is manually measured from the beginning of the P wave deflection from the isoelectric line to the end of the deflection returning to isoelectric line in all simultaneous 12 leads of a standard paper-printed ECG. Therefore, PWD results from the difference between the shortest and the longest P wave duration in any of the simultaneous 12 ECG leads (Figure 1). PWD can be calculated

by measurements on paper or computerized methods. However, manual measurement of P wave duration is feasible, more stable and reliable when performed on the high-resolution screen of a digital ECG system: scanning and digitizing paper-printed ECGs allow to achieve greater precision in detecting and measuring PWD.⁶

Increased PWD values reflect the inhomogeneous propagation of sinus impulses and the prolongation of atrial conduction time, a recognized electrophysiological substrate in patients with paroxysmal AF. PWD was proven to be a sensitive and specific ECG marker for the risk of AF occurrence with a cutoff value of 40 ms for the identification of patients with history of paroxysmal lone AF in comparison with healthy subjects.⁵ Various insults leading to atrial remodeling result in slowed atrial conduction with inhomogeneous recovery, reflecting prolonged, inhomogeneous and anisotropic distribution of connections between atrial myocardial fibers.⁷ PWD may be particularly relevant to cryptogenic stroke where high PWD values could originate from multiple inflammatory insults directed against atrial myocardial cells.⁸ In fact, in patients with cardioembolic stroke and paroxysmal AF, increased PWD values has been consistently reported (Table 1).^{3,9} Furthermore, in our own previous study³ showed that PWD values in cryptogenic stroke, as well as in cardioembolic group, are higher in comparison with healthy subjects, suggesting that PWD may be a marker to identify groups of patients to submit to longer ECG monitoring. Similarly, in recurrent transient ischemic attacks, high PWD values were observed, suggesting that a PWD>40 msec may be linked to an underlying silent paroxysmal AF, possible cause of ischemic recurrence.¹⁰ Another recent stu-

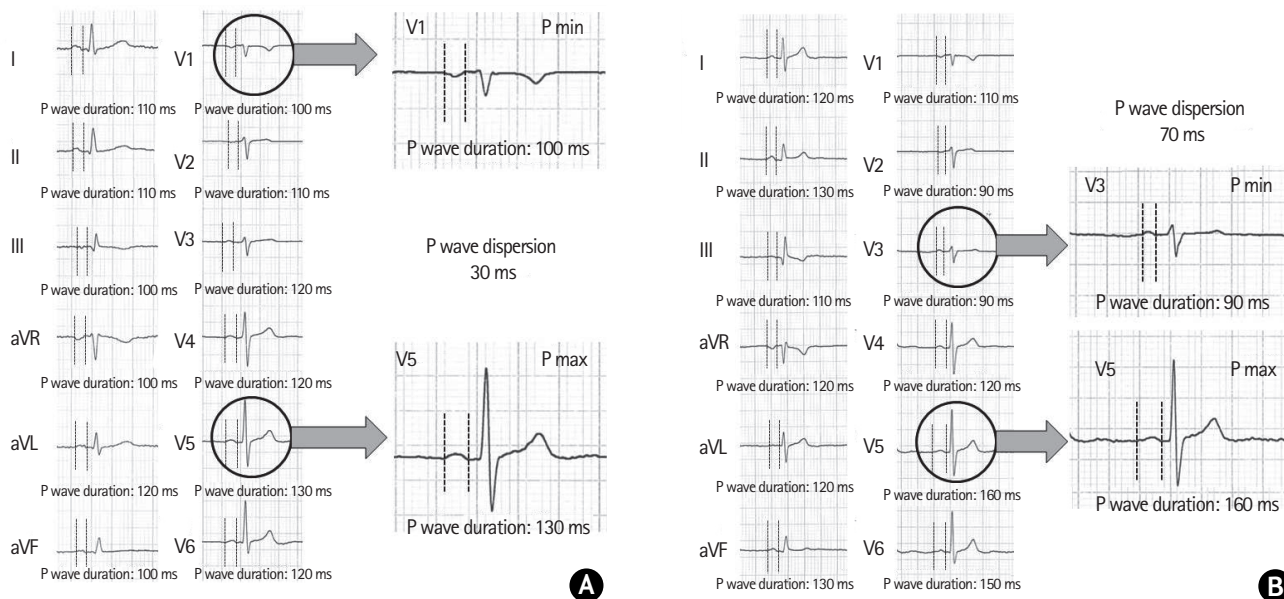


Figure 1. Examples for measurement of P wave duration in 12 leads of two standard digitized paper-printed electrocardiogram (ECG) (A: healthy subject. B: patient with cryptogenic stroke). P wave duration is measured from the beginning of the P wave deflection from the isoelectric line to the end of the deflection returning to isoelectric line in all simultaneous 12 leads of ECG. P wave dispersion results from the difference between the shortest (P minimum) and the longest (P maximum) P wave duration.

Table 1. Clinical studies on P wave dispersion in patients with stroke

Author (year)	Subjects evaluated		Age (years)		Patients and control group characteristics		P wave dispersion (msec)		
	Patient group	Control group	Patient group	Control group	Patient group	Control group	Patient group	Control group	P
Kocer et al. (2009) ¹²	67	58	64±12	61±7	Non-cardioembolic strokes	Healthy subjects	45±20	43±12	n.s.
Dogan et al. (2012) ⁹	40	40	69±12	69±13	Ischemic strokes with PAF	Ischemic strokes without PAF	65±14	50±12	<0.001
Acampa et al. (2015) ³	108	35	67±14	66±9	Cryptogenic strokes	Healthy subjects	46±12	33±8	<0.05
Vural et al. (2015) ¹¹	40	40	41.9±6.7	42.5±7.1	Cryptogenic strokes	Healthy subjects	30.1±7	27.4±3.5	0.02

Values are expressed as mean±standard deviation. PAF, paroxysmal atrial fibrillation; n.s., not significant.

dy¹¹ demonstrated increased PWD values in cryptogenic stroke patients, also suggesting an association with impaired left atrial mechanical functions and atrial enlargement, involved in the pathophysiology of AF. Conflicting results were reported by a previous study only,¹² which found no difference in PWD values in acute stroke patients vs. control group. However in this study, patients with history of AF and cardiac diseases were excluded. Moreover, pathogenesis of ischemic strokes was not reported. PWD represents a promising marker of AF occurrence in these patients and a useful tool to identify subjects needing prolonged ECG monitoring; however, since these small reported studies didn't evaluate the correlation between this ECG marker and future detection of AF in cryptogenic stroke, further prospective studies are needed, in order to evaluate the relationship between

PWD values and AF detection during prolonged ECG monitoring.

Finally, in our recent paper,⁴ we suggested that 12-lead resting ECG represents a great potential tool in the evaluation of patients with cryptogenic stroke, because, besides PWD, ECG may show other P wave indices, such as P wave duration above 120 ms and PR interval greater than 200 ms. These indices provide important information on atrial electric abnormalities during sinus rhythm: they reflect subclinical atrial remodeling, secondary to the cumulative exposure to heterogeneous insults, representing a substrate for AF.

References

1. Bridge F, Thijs V. How and when to screen for atrial fibrilla-

- tion after stroke: insights from insertable cardiac monitoring devices. *J Stroke* 2016;18:121-128.
2. Saver JL. Clinical practice. Cryptogenic stroke. *N Engl J Med* 2016;374:2065-2074.
 3. Acampa M, Guideri F, Tassi R, Dello Buono D, Celli L, di Toro Mammarella L, et al. P wave dispersion in cryptogenic stroke: a risk factor for cardioembolism? *Int J Cardiol* 2015;190:202-204.
 4. Acampa M, Lazzerini PE, Martini G. Letter by acampa et al regarding article, "Underutilization of ambulatory ECG monitoring after stroke and transient ischemic attack: missed opportunities for atrial fibrillation detection". *Stroke* 2016;47:e277.
 5. Dilaveris PE, Gialafos JE. P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. *Ann Noninvasive Electrocardiol* 2001;6:159-165.
 6. Dilaveris PE, Gialafos JE. P-wave duration and dispersion analysis: methodological considerations. *Circulation* 2001;103:E111.
 7. Okutucu S, Aytemir K, Oto A. P-wave dispersion: what we know till now? *JRSM Cardiovasc Dis* 2016;5:2048004016639443.
 8. Acampa M, Lazzerini PE, Guideri F, Tassi R, Martini G. Ischemic stroke after heart transplantation. *J Stroke* 2016;18:157-168.
 9. Dogan U, Dogan EA, Tekinalp M, Tokgoz OS, Aribas A, Akilli H, et al. P-wave dispersion for predicting paroxysmal atrial fibrillation in acute ischemic stroke. *Int J Med Sci* 2012;9:108-114.
 10. Koz C, Uzun M, Yokusoglu M, Ulas UH, Baysan O, Genc C, et al. Echocardiographic, electrocardiographic, and clinical correlates of recurrent transient ischemic attacks: a follow-up study. *South Med J* 2008;101:246-251.
 11. Vural MG, Cetin S, Yilmaz M, Akdemir R, Gunduz H. Relation between left atrial remodeling in young patients with cryptogenic stroke and normal inter-atrial anatomy. *J Stroke* 2015;17:312-319.
 12. Kocer A, Barutcu I, Atakay S, Ozdemirli B, Gul L, Karakaya O. P wave duration changes and dispersion. A risk factor or autonomic dysfunction in stroke? *Neurosciences (Riyadh)* 2009;14:14-18.
-
- Correspondence:** Maurizio Acampa
 Department of Neurological and Sensorineural Sciences, General Hospital "Santa Maria alle Scotte", Azienda Ospedaliera Universitaria Senese, viale Bracci, n.1, 53100 Siena, Italy
 Tel: +39-577585476
 Fax: +39-577586294
 E-mail: M.Acampa@ao-siena.toscana
- Received: October 22, 2016
 Revised: March 8, 2017
 Accepted: March 10, 2017
- The authors have no financial conflicts of interest.
-