

Advances in Arrhythmia and Electrophysiology

P Wave Indices

Current Status and Future Directions in Epidemiology, Clinical, and Research Applications

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Our review describes the current field of P wave indices. We report the methodology for determining P wave indices. We also describe the strengths and limitations of the current literature on the clinical correlates and prognosis of P wave indices. We suggest future clinical and research directions for P wave indices.

The P wave indices of maximum duration and dispersion have received increasing attention and have been examined in a broad range of clinical settings. The ECG, as a vectorcardiogram,¹ quantifies the magnitude and direction of electric propagation and depolarization. Insults such as chronically elevated atrial pressure, ischemia, and metabolic stress lead to atrial remodeling marked by inflammation, fibrosis and poor cellular coupling. The electrophysiological result is slowed conduction with inhomogeneous recovery, defining a substrate for atrial fibrillation (AF).²

Investigators hypothesize that P wave prolongation is an intermediate step in the accumulation of insults ultimately leading to AF. Thus, initial studies sought to demonstrate significant differences between samples with a history of AF and healthy referents, arguing that prolonged P wave duration and dispersion predict recurrent AF. Further studies have used P wave indices to compare multiple samples with and without cardiac diseases. The most recent iteration of studies has extended use of P wave indices beyond cardiac pathology to distinguish a variety of disease entities and comparison groups; the wide array of disease samples studied is listed in Table 1. Given such broad clinical applications, automated reporting of the P wave duration in electrocardiographic measurement for screening purposes has been advocated.⁴¹

The variety of studies has resulted in varying methodologies and yielded conflicting results. Many areas in P wave indices research remain uncertain, including their clinical correlates and distribution in the community, and the extent to which P wave indices are associated with AF, predict its occurrence, are heritable phenotypes, or serve as biomarkers

of other cardiovascular insults. The present review was undertaken to assess the current evidence for use of P wave indices with attention toward study design, strengths, and remaining questions surrounding their clinical application.

Literature Search Methods

We conducted a literature search of PubMed and OVID databases to identify articles published from January 1985 to December 2007. We searched using the Medical Subject Headings and key words of P wave dispersion, P wave indices, dispersion, AF, and ECG, both separately and together with predict and prediction. We reviewed reference lists of retrieved articles to identify additional publications for inclusion. Because of the volume of research in this area and the duplicative nature of the field's research, we excluded studies with less than 100 subjects unless they described a novel clinical application of P wave indices. Studies were described as cohort, case control, or cross-sectional. Case reports, scientific abstracts and articles published in languages other than English were excluded.

Measurement and Reproducibility of P Wave Indices

Quantification

Maximum and minimum P wave durations are calculated from the standard ECG during sinus rhythm. P wave dispersion is derived by subtracting the minimum P wave duration from the maximum in any of the 12 ECG leads. The term dispersion in the context of P wave indices describes atrial conduction and not the repolarization conveyed by T-wave dispersion. Some studies report visualizing P wave onset and offset in a minimum of 8 to 9 leads as an inclusion criterion, although a minimum of 3 leads has been used to determine P wave duration.²³

We did not identify a report examining correlations of P wave indices measured in different electrocardiographic

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Table 1. Clinical Conditions Studied Utilizing P Wave Indices

Risk factors	Hypertension ³⁻⁵ Obesity ⁶⁻⁹ Diabetes ¹⁰
Noninvasive measures	Diastolic indices ^{3,11}
Miscellaneous conditions	Hemodialysis ¹² Hyperthyroidism ¹³ Rheumatoid arthritis ¹⁴ Scleroderma ¹⁵ Pregnancy ¹⁶ Obstructive sleep apnea ¹⁷
Cardiovascular disease	Aortic stenosis ¹⁸ Mitral stenosis and balloon valvuloplasty ¹⁹ Secundum atrial septal defect, before and after surgical repair ^{20,21} Post-Fontan procedure ²²
Atrial fibrillation	Incident AF ²³⁻²⁸ Following pacemaker implantation ^{29,30} Recurrence postcardioversion ³¹ Postcoronary artery bypass graft surgery ³²⁻³⁴ Postthoracic surgery ³⁵ Ischemia or angina ³⁶⁻³⁸ Atrioventricular nodal reentry tachycardia and ablation ³⁹ Accessory pathway and ablation ⁴⁰

leads. Currently, P wave indices are calculated from the absolute difference between the shortest and longest P waves from the surface ECG. Use of adjacent leads with shared vectorial orientation may provide greater sensitivity for distinguishing the inhomogeneity of atrial activation. Future studies should analyze lead heterogeneity in findings, and report results highlighting the lead(s) from which they were derived.

The large majority of studies used the P wave of longest or shortest duration; few studies determined a mean value from

multiple measurements.^{6,40} The largest studies (n=500 to 1353) to examine the relation of P wave duration and dispersion showed correlations ranging from 0.42⁴² to 0.66.⁴³

P wave indices have been calculated by measurements on paper or digitized images. Manual measurement with calipers has entailed increasing the ECG rate to 50 mm/s and the voltage to 1 to 2 mV/cm,^{24,44} accompanied by use of magnification. There is potential for discrepancy in the 2 methods, and as reviewed below, the data consistently demonstrate that hand-held caliper measurements have less accuracy compared with digital measurements.⁴⁴ The Figure demonstrates measurement of P wave indices in a normal ECG at 25 mm/s using a digital measurement technique. Reliability of P wave indices calculation requires accurate determination of the P wave on-set and off-set.

Reproducibility

Comparing paper and digital measurements, for maximum P wave duration measurements, the intraobserver relative errors were reduced from 16% to 7% and the interobserver relative errors were diminished from 17% to 8%. Similarly, the relative errors for P wave dispersion were reduced from 24% to 13% for intraobserver, and from 30% to 14% for interobserver comparing paper and digital measurement acquisition.²⁵

The literature has varied in reproducibility metrics reported. Studies have described mean interobserver percent error ranging from 2%²⁶ to 14%.²⁵ Coefficients of variation have ranged from 2%³⁹ to 5%.²⁴ Intraobserver reproducibility has been shown to be strong, with correlation coefficients ranging from $r=0.78$ ²⁷ to $r=0.97$.⁴⁵

Distribution of P Wave Indices Reported in the Literature

The distribution of P wave indices has been studied in community, ambulatory, and hospitalized cohorts. Table 2 describes representative studies of P wave indices reported in the literature, including measurements reported for the referent or control cohorts from selected studies. For most of these studies, referent cohorts are comprised of matched patients serving as controls. In these studies the maximum P wave

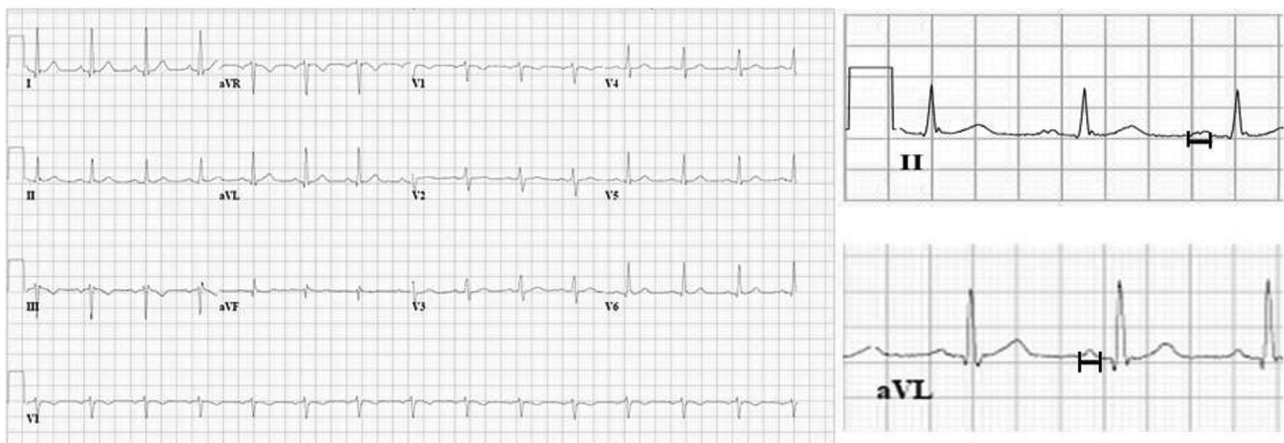


Figure. Twelve-lead ECG with normal sinus rhythm and normal intervals. Measurement by digital calipers of leads II and aVL (side panels) demonstrated maximum and minimum P wave durations, respectively: 128 and 85 ms, with resulting P wave dispersion 23 ms.

Table 2. Summary of P Wave Indices in Referent Cohorts and Selected Studies

Author	Study Design; Clinical Context	N (Referent or Control Cohort)	Maximum P Wave Duration, ms; (Range)	P Wave Dispersion, ms; (Range)
Dilaveris et al ²⁷	Cross-sectional; PAF	40	101.0±10.0	28.0±7.0
Andrikopoulos et al ²⁵	Cross-sectional; PAF	50	101.4±10.1	29.8±8.7
Aytemir et al ²⁴	Cross-sectional; PAF	70	101.0±11.0	27.0±10.0
Tukek et al ⁴⁶	Cross-sectional; COPD	33	93.0±13.0	39.0±7.0
Gialafos et al ⁴³	Military cohort, young men	1353	96.0±11.0 [62.0–142.0]	38.0±10.0 [13.0–80.0]
Guray et al ²⁰	Cross-sectional; ASD	47	102±13	31±9
Turhan et al ¹⁸	Cross-sectional; AS	98	108.0±7.0	32.0±5.0
Yigit et al ²⁶	Observational study; impact of exercise on P wave indices	155	94.0±2.3	52.1±2.0
Gunduz et al ¹¹	Cross-sectional; diastolic dysfunction	60	104±9	43±9
Ariyarahaj et al ⁴⁷	Cross-sectional; ambulatory patients	469	[40–170]	
Dagli et al ³	Cross-sectional; hypertension	60	64±10.2	30.3±6.6
De Bacquer et al ²⁸	Nested case-control	120		
Lauer et al ⁴⁸	Prospective following CABG	8166		

PAF indicates paroxysmal atrial fibrillation; CABG, coronary artery bypass graft.

duration ranged from 93 ± 10^{46} to 108 ± 7.0^{18} ms. P wave dispersion ranged broadly from 27 ± 10^{24} to 52 ± 2^{26} ms. In the largest identified community study of 1353 healthy air force servicemen, mean age 24 years (range 18 to 41), the mean maximum and minimum P wave durations were 95.6 and 57.2 ms, respectively.⁴³ P wave dispersion mean was 38.4 ms, range of 13 to 80 ms; the median was not reported. In the same cohort the P wave duration prevalence ≥ 110 ms was 9.1% and ≥ 120 ms was 1.6%.⁴⁹ A large, prospective cohort (n=8166) of patients after coronary artery bypass surgery had a median P wave duration of 112 ms (interquartile range 100 to 120 ms).⁴⁸

Although the criteria for abnormal P wave indices vary by study, several investigators have examined the prevalence of P wave duration exceeding various cutpoints. The prevalence of P wave duration ≥ 110 ms has been estimated as high as 41%,⁵⁰ and ≥ 120 ms as high as 47%⁵¹ in hospitalized samples prompting the description of this finding as “pandemic”.⁵² A community-based sample of individuals ≥ 65 years identified 400 of 678 (59%) subjects as having a P wave duration ≥ 110 ms.⁵³ The prevalence among men and women was similar (58.5% and 59.4%, respectively). Before coronary artery bypass surgery 56% of patients (868 of 1553 subjects) had a P wave duration > 110 ms.³² Screening for P wave duration ≥ 120 ms increases the specificity of identifying prolonged P wave duration.⁴⁷

In summary, studies suggest a large range for P wave indices in the community and ambulatory settings, with an increased prevalence of prolonged P wave indices with advancing age. To our knowledge, no large, community-based study has described the distribution of P wave indices in a reference sample without disease or risk factors, and then applied these values to define the range in a broad sample.

Clinical Correlates Associated With P Wave Dispersion

Demographics

We are unaware of prior studies that have systematically examined the relations of P wave indices with a broad range

of clinical risk factors; rather the studies have tended to examine one risk factor at a time. Most previous studies have reported that P wave duration increases with advancing age.⁵¹ However, because most prior studies have not adjusted for the increases in risk factors and disease that occur with advancing age, it is uncertain whether aging per se increases P wave indices. Men and women in an older population (≥ 65 years) have been shown to have equivalent prevalence of P wave duration ≥ 110 ms.⁵³ Similarly, ethnic/racial differences in P wave indices have been understudied.

Risk Factors

Cross-sectional studies have examined the relations between risk factors and P wave indices. Subjects with uncontrolled hypertension have been shown to have significantly prolonged P wave duration and dispersion.³ In an unadjusted cross-sectional case-control study subjects with diabetes (n=76) had significantly longer P wave indices than controls (n=40).¹⁰ Several studies have examined the relations of P wave indices to obesity and have shown individuals with obesity had significantly longer P wave indices compared with control groups.^{7,8} Body mass index was moderately correlated ($r=0.50$) with P wave dispersion,⁷ even in analyses adjusting for other clinical variables.⁸ Of interest, a decrease in P wave indices has been observed after weight loss.⁶ Similarly, bariatric surgery in a severely obese cohort was associated with a significant reduction in P wave indices over a 12-month period.⁹

Subclinical and Clinical Cardiac Disease

Cross-sectional studies have assessed diastolic function and P wave indices and associated diastolic dysfunction with prolonged P wave indices compared with referent cohorts.^{3,11} P wave indices and diastolic dysfunction may comprise markers of a common pathophysiologic process. P wave indices and diastolic dysfunction may influence each other in a bidirectional fashion, one may predispose to the other, or their association may be due to confounding resulting from a more complex pathophysiologic process. The associations

identified by these studies raise multiple hypotheses which merit further elucidation.

Studies meeting inclusion criteria examining P wave indices and coronary syndromes ranged in size from 95³⁶ to 147 individuals.³⁷ P wave dispersion before and after coronary intervention decreased from 69.5 to 52.4 ms.³⁸ These values are substantively longer than those reported by the other identified studies^{36,37} evaluating the association between P wave indices and ischemia.

P wave indices have been examined in structural and valvular disease. They were significantly longer in subjects with aortic stenosis compared with controls.¹⁸ A single-center, case control study identified a significant decrease in P wave indices at 1 month after mitral balloon valvuloplasty for mitral stenosis.¹⁹ Similarly, subjects with a secundum atrial septal defect have had longer maximum P wave duration and P wave dispersion compared with matched controls²⁰; surgical repair of atrial septal defects has resulted in regression of P wave indices.²¹

Noncardiac Conditions

Studies have examined P wave indices in a variety of noncardiac conditions. The largest identified study (n=32) examining the effect of hemodialysis on P wave indices reported that maximum P wave duration and P wave dispersion increased significantly postdialysis.¹² A study reported that individuals with hyperthyroidism (compared with euthyroid individuals) had greater baseline maximum P wave duration and P wave dispersion, and that hyperthyroidism suppressive therapy was associated with a decrease in indices.¹³ Other efforts have determined positive association between P wave indices and rheumatoid arthritis¹⁴ or scleroderma.¹⁵ A larger, single-center study compared P wave indices of 162, healthy pregnant women with 150 matched controls,¹⁶ and found the pregnant cohort had a decreased minimum P wave duration.

Summary of Clinical Correlates

P wave indices have been evaluated in multiple clinical contexts including cardiac and noncardiac disease states. Of particular interest are the relations between prolonged P wave indices and advancing age, hypertension, diabetes, and obesity, each of which has been identified as an independent risk factor for AF.^{54–56} Increased atrial pressures due to structural heart disease also clearly potentiate prolongation of P wave indices. These disease states may share common pathways of atrial inflammation and fibrosis⁵⁷ that yield to atrial remodeling and inhomogeneity of conduction.

The investigations of P wave indices with clinical correlates, cardiovascular and noncardiac conditions have limitations. Most studies were small to moderate in sample size, involved referral cohorts, and consequently had limited power and generalizability. Furthermore, the cross-sectional studies generally did not assess for either confounding or effect modification between advancing age, and clinical correlates in relation to P wave indices. The long-term impact of treating most risk factors or disease states such as hypertension and diabetes has not been assessed systematically and

merits elucidation. Multiple clinical correlates in the community have yet to be investigated.

Electrocardiographic and Electrophysiological Correlates of P Wave Indices

Electrophysiological studies have demonstrated significantly increased effective refractory periods, conduction times, and heterogeneity in right atrial conduction in older patients with no history of AF compared with younger cohorts.⁵⁸ Consistent with prior studies the investigators noted a positive correlation ($r=0.60$) between mean age and P wave duration (measured only in lead II).⁵⁸ Slowed interatrial conduction velocity has been demonstrated in a similarly small cohort with a history of AF.⁵⁹ P wave loops may have an application toward further predicting risk of AF. Modification of P wave loops, and electroanatomical descriptions of P wave propagation, have been demonstrated by pulmonary vein isolation.⁶⁰

Limitations included small sample sizes, lack of adjustment for covariates, and cross-sectional design. However, these studies generate hypotheses about pathways involving aging, inflammation and other insults resulting in atrial fibrosis, and the accompanying increased atrial heterogeneity reflected in prolonged P wave indices. Such a nuanced phenotypic model is perhaps more descriptive of P wave prolongation than describing P wave prolongation as “interatrial block,” and distinguishes electrophysiological atrial activity from atrial size; atrial fibrosis is not indicative of atrial enlargement.

The electrocardiographic correlates of P wave indices are incompletely described. Our search did not identify studies assessing the relations of P wave indices with PR interval or QRS duration. Heart rate (ie, RR interval) had a significant but modest association with P wave duration ≥ 110 ms in a large cohort of healthy young men (odds ratio 1.027 per bpm, 95% confidence interval 1.01 to 1.04)⁴⁹ A clinical trial assessing the effect of exercise on P wave indices control subjects had a slight decrease in mean P wave duration (94.0 to 92.1 ms) and increase in mean dispersion (52.1 to 53.0) between rest and peak exercise.²⁶

Signal Average ECG

Signal average ECGs (SAECG) have been used for predicting AF. Applications of SAECG are similar to P wave indices’ described above. Prolonged P wave SAECGs have been associated with recurrence of AF after cardioversion⁶¹; comparison of hypertensive subjects with paroxysmal AF and those without⁶²; AF after cardiothoracic surgery^{63,64}; and transition from paroxysmal to permanent AF.⁶⁵ Advantages of SAECG include its incorporation of information from hundreds of data points and lack of reliance on distinguishing P wave on-set and off-set, which improve the reliability and accuracy of the technique. Disadvantages of P wave SAECG are that it requires high fidelity, and highly specialized equipment that is not in wide clinical usage. The need for patients to lie completely still for 3 to 5 minutes in a room with no electric interference also limits its broad implementation.

Genetic Variation and P Wave Indices

We were unable to find studies describing the heritability or genetic associations of P wave indices. In contrast, PR interval has been demonstrated as a heritable phenotype and has been associated with genetic variants in a community-based genome wide association study.⁶⁶ Understanding the genetic contribution toward variability of P wave indices may provide endophenotypes or intermediate traits, which will aid in dissecting the contribution of genetic variation to inhomogeneous of atrial conduction. Such an investigation may be combined with results from other genome wide association studies that have examined genetic variants and AF,⁶⁷ and may contribute insights into pathophysiology and propensity for the development of AF.

P Wave Indices and AF

Much of the literature on P wave indices has focused on their association with AF. Selected studies meeting the inclusion criteria for this review and pertinent to P wave indices and AF are summarized in Electronic Supplement Table 1. Cross-sectional studies have identified significantly prolonged P wave indices in individuals with a documented history of AF compared with a control cohort with no history of AF.^{24–27}

P Wave Indices and AF Recurrence

Subjects with recurrent AF have been shown to have significantly longer P wave indices and longer documented history of AF duration compared with individuals that maintained sinus rhythm. The largest cohort study included 64 subjects, and found the 28 with recurrence had significantly longer P wave indices.³¹

Association With Incident AF

Prolonged P wave indices have been associated with increased risk for incident AF. A retrospective cohort study followed 97 patients with essential hypertension for a mean duration of 25 ± 3 months, identifying incident AF in 20%.⁴ Adjusting for age attenuated the odds ratio from 2.09 to 1.34 for prolonged P wave indices (maximum duration ≥ 130 ms and dispersion ≥ 40 ms) to predict AF. In a case-control study of 308 hospitalized subjects, the prevalence of P wave duration ≥ 110 ms was 52% in the cohort with AF, compared with 18% of the 308 subjects in a referent cohort.²³ This study had a large age range (26 to 93 years) and calculated P wave duration from 3 leads. A nested case-control study from a population-based study found that 70% of 40 elderly subjects who developed AF after 10 years had baseline P wave durations >120 ms, compared with 41% of the 120 controls.²⁸ P wave duration remained predictive of AF after adjustment for covariates of body mass index and hypertension. Finally, in a prospective cohort of patients presenting with myocardial infarctions, patients whose presentation was complicated by AF had longer P wave indices.³⁷

P Wave Indices and Association With AF After Cardiothoracic Surgery

AF after cardiac surgery is associated with significant morbidity from prolonged hospitalization and an array of complications.⁶⁸ Three retrospective studies examined P wave

indices before cardiothoracic surgery to determine their relation to AF.^{32–34} The studies ranged in size from 120³⁴ to 1553,³² and analyzed P wave duration as >100 or 110 ms. In multivariable analysis increased P wave duration was a significant predictor of AF.^{32,33} In a single center cohort analysis of 300 patients, mean P wave duration increased significantly after bypass surgery and predicted postoperative AF in multivariable analysis.³³ Median P wave dispersion was similarly prolonged after thoracic surgery in a cohort which developed AF.³⁵ In the cardiac surgery studies age,³⁴ body surface area,³³ prior AF or low cardiac output³² had a greater odds ratio for predicting postoperative AF than P wave duration.

Pacing Cohort

Studies have examined P wave indices and the development of AF in cohorts with pacemakers. P wave indices, paced or nonpaced, did not predict AF in 109 subjects with sick sinus syndrome.²⁹ A large ($n=660$), prospective observational study followed a cohort paced for sinus bradycardia and found prolonged P wave indices were associated with AF hospitalization.^{29,30} Furthermore, subjects with longer P wave duration (≥ 100 ms) had significantly longer paced P wave durations.

P Wave Indices, Other Dysrhythmias, and Incidence of AF

In unique small ($n=72$ and 78) studies of individuals referred for electrophysiological study of atrioventricular nodal re-entry tachycardia³⁹ or accessory pathways⁴¹ subjects with a history of AF had significantly greater maximum P wave duration and P wave dispersion.

Summary of Relation of P Wave Indices to AF

Larger, more clinically robust studies with longer follow-up are necessary to determine the clinical relevance of P wave indices to incident AF. Limitations in the studies described earlier include lack of adjustment for covariates, short duration of follow-up, small to moderate sample sizes, and treatment of P wave duration as a binary trait rather than a continuous variable.

Conclusion

Summary

P wave indices have been applied in a wide range of clinical contexts. They have been associated with clinical risk factors for AF, recurrence and incident AF in small to moderate sized referral cohorts of individuals with risk factors, structural heart disease or undergoing cardiothoracic surgery. The current research on P wave indices has been limited by studies with modest sample size, cross-sectional or limited follow-up, and lack of accounting for confounders. Most studies referenced in Table 1 have less than 100 subjects.

Despite the volume of studies, P wave indices reference (“normal”) values have not been standardized. P wave duration cut-offs of 110 or 120 ms have been proposed, but the large prevalence of hospitalized patients found to meet these criteria suggests a low specificity and poor screening utility. No prospective, community-based study has developed ref-

erence values by identifying a reference population, articulating measurements of indices, and then applying those measurements to a broad sample with cardiovascular disease, risk factors, and the covariates identified here.

Measurement techniques have not been standardized. Investigators continue to use magnification and hand-held calipers, yet have reported measuring P wave duration to the hundredth of a millisecond with this technique. A single study compared measurement techniques and found improved quality control with digitized measurements.⁴⁴ Quality control assessments have been limited. Most investigators used measurements surrounding the mean, potentially inflating reproducibility. Robust statistical measures for vigorous quality control are lacking. The deficits of standardized techniques and quality control severely limit the application of P wave indices.

Substantive questions remain concerning the correlations of calculated P wave indices and invasive electrophysiological studies. Agreement between these 2 methods will be essential to verify the validity of P wave indices. There has not been adequate comparison of SAECG and P wave indices. Finally, interlead heterogeneity has not been incorporated into the assessment of P wave indices.

Future Research Directions

Significant challenges remain with regard to our implementation of P wave indices as a relevant component of screening. Reference values from large, community-based studies will assist with standardizing indices for sex and height. Correlations with heart rate, PR interval, and QRS duration will assist with understanding the electrocardiographic significance and interrelation of electrocardiographic parameters.

To date, no direct study between P wave SAECG and P wave indices has been performed; such a comparison will be an important advance for the field. Comparing P wave indices and data from electroanatomical mapping will elucidate the correspondence between a noninvasive and invasive assessment of atrial electrophysiology. Such an undertaking has the potential to demonstrate further the utility of P wave indices for screening purposes.

Clinical correlation with cardiac and noncardiac disease states with attention to the influence of advancing age will provide further insights. For instance, cohort studies examining the associations of multiple cardiovascular risk factors and P wave indices will validate the findings of studies described in this review. Echocardiographic and MRI features also will assist with determining the impact of structural heart diseases on P wave indices. P wave indices may be heritable traits, and provide valuable endophenotypes to contribute to the research community's understanding of the genetic basis of electrocardiographic and electrophysiological traits.

The utility of P wave indices as a clinically useful biomarker remains ambiguous. The chief question in establishing the relevance of a biomarker is whether such a measurement merely reflects pathophysiologic processes or provides unique, complementary insights to predict adverse outcomes. Large size, community-based cohort studies are necessary to achieve adequate power and adjustment for

covariates. Such an effort will determine the utility of P wave indices to predict incident AF, heart failure, and overall mortality, and whether they provide additional data beyond already established clinical, echocardiographic and electrocardiographic covariates. P wave indices have potential to influence the treatment of AF. P wave indices may predict success with strategies such as elimination of triggers, ie, pulmonary vein isolation, or substrate modification by pharmacological intervention and risk factor management. Inexpensive and noninvasive, P wave indices may provide a cost effective screening mechanism. Further research is necessary to establish whether P wave indices will contribute independent information toward the ability predict the development of AF, adverse cardiovascular outcomes, and mortality.

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Disclosures

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